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DIHYDROCODEINE*

Further Development in Measurement of Analgesic Power and Appraisal of Psychologic Side Effects of Analgesic Agents

JOACHIM S. GRAVENSTEIN, M.D.,† GENE M. SMITH, PH.D.,‡ RAYMOND D. SPHIRE, M.D.,§
JAMES P. ISAACS, M.D.,¶ AND HENRY K. BEECHER, M.D.‖

BOSTON

DIHYDROCODEINE and dihydroisocodeine are hydrogenated derivatives of codeine and isocodeine. Eddy and Small[1] investigated the toxicity and analgesic potency of the two isomers in animals. As with codeine, both drugs in mice and rabbits produced initial central-nervous-system depression. The doses required were smaller than those for codeine. A further increase in the dosage of dihydrocodeine resulted in convulsions. Dihydroisocodeine in large dosage did not produce convulsions at all. Analgesic potency was measured in cats by the tail-pressure method. Both dihydroisocodeine and dihydrocodeine produced greater analgesia than codeine, milligram for milligram. These agents were thus candidates for clinical trial.

In the present study dihydroisocodeine and dihydrocodeine were evaluated for their analgesic power in patients and for side-effect liability in healthy volunteers. It would have been desirable, of course, to investigate the side actions of analgesic drugs in patients. This presents practical difficulties that we have not yet satisfactorily overcome for the postoperative patients whom we use in evaluating analgesic power. This problem has been discussed elsewhere.[2]

METHODS

Analgesia

Evaluation of the analgesic potency of these two drugs was carried out in three phases: in the first two, by the technic and principles described in earlier papers[2,3] and in the third by a modification of that technic. In the first phase dihydroisocodeine, 15 and 30 mg., was studied (Table 1, Group A). Three years later, in the second and third phases, dihydroisocodeine, 15, 30 and 60 mg. (Table 1, Group B), and dihydrocodeine, 15, 30 and 45 mg. (Table 2), were tested. The bitartrate salt of the codeine derivatives and the phosphate salt of the morphine standard were used. All weights given refer to the salts. They are stated for 70 kg. of body weight. All solutions were prepared to contain the dosage for 70 kg. of body weight in 1 ml. All doses were injected subcutaneously.

Patients from the general surgical wards were studied postoperatively to determine relief of steady wound pain. Before the medication was given every patient was required to rate the pain as "bearable" (moderate pain) or "severe." Patients reporting slight pain, or pain occurring only on motion, did not qualify for the study. Medication against pain was given only on the patient's request, but not within the first two hours after a previous medication for pain.

Each patient received morphine, 10 mg. per 70 kg. of body weight, alternating with the doses mentioned above of dihydroisocodeine or dihydrocodeine. The order of administration of the drugs was alternated from patient to patient. The drugs were given as unknowns by code to the patients, and evaluation of relief was made by technicians unaware of the nature of the medications.

After a drug was given the patients were visited by the technicians at regular intervals. Records were made of whether their pain had remained unchanged (no relief), had improved, but was less than half gone (poor relief), had improved and was more than half gone (good relief) or had disappeared (complete relief). In the first and second phases the patients were visited at forty-five and ninety minutes after medication. In the third phase this observation period was

*From the Anesthesia Laboratory of Harvard Medical School at the Massachusetts General Hospital.

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†Research associate in anesthesia, Harvard Medical School; fellow in anesthesia, Massachusetts General Hospital.

‡Research associate in anesthesia, Harvard Medical School; research fellow in anesthesia, Massachusetts General Hospital.

§Formerly, assistant resident in anesthesia, Massachusetts General Hospital.

¶Resident in surgery, Johns Hopkins Hospital, Baltimore; formerly, assistant resident in anesthesia, Massachusetts General Hospital.

‖Dorr Professor of Research in Anaesthesia, Harvard Medical School.

prolonged to a maximum of six hours, checks being made at forty-five, ninety, one hundred and twenty, one hundred and eighty, two hundred and forty, three hundred and three hundred and sixty minutes after medication, unless pain recurred within this six-hour period and the patient requested medication.

After medication some patients fell asleep. For the first two checks, at forty-five and ninety minutes after medication, they were aroused to be questioned about their pain. In the third phase of the study, on the consecutive checks, they were awakened if necessary at forty-five and ninety minutes but not at two, three, four, five and six hours after medication. Since we had no way of telling whether a sleeping patient was a pain-free patient, the "sleepers" were treated separately.

TABLE 1. *Relief of Pain from Dihydroisocodeine As Compared with Standard Dose of Morphine.*

GROUP	NO. OF PATIENTS	DOSE OF DIHYDRO-ISOCO-DEINE	RELIEF OBTAINED	DOSE OF MOR-PHINE	RELIEF OBTAINED	RELIEF OBTAINED WITH DIHYDROISO-CODEINE MINUS MORPHINE
		mg.	%	*mg.*	%	%
A	12	15	61.1	10	72.2	−11.1
	30	30	73.9	10	69.6	+ 4.3
B	27	15	63.0	10	72.0	− 9.0
	35	30	68.0	10	68.0	± 0
	26	60	72.0	10	72.0	± 0
C*	39	15	62.0	10	72.0	−10.0
	65	30	71.0	10	69.0	+ 2
	26	60	72.0	10	72.0	± 0

*Figures from Groups A and B combined.

Only "paired" data were employed for comparison of pain-relieving power — that is, doses of morphine and one of the other analgesic agents were administered to the same patient as successive medications for pain. Patients who received more than one pair of doses were given an average relief score, expressed as percentage, for each drug. The criterion for significant relief was arbitrarily defined as "pain completely relieved or more than half gone" at the two first checks forty-five and ninety minutes after medication (Tables 1, 2 and 3). Relief of 50 per cent or more is interpreted by the patient as of great degree. It is a judgment patients find easy to make, as indicated by consistency and the reproducibility of findings not only in our hands but also in other laboratories where this approach is now used.

In the evaluation of dihydrocodeine, 30 mg., in the third phase (Tables 3 and 4), patients reporting "moderate" pain and patients reporting "severe" pain were analyzed separately, for control of the variable of pain level. The desirability of controlling the variable of pain level is indicated by the fact that the ratio of severe to moderate pain decreases rapidly during the first twenty-four hours after surgery (Table 5).

Physical Side Actions

The side-action liability of the drugs under investigation was studied in a first group of 10 healthy male volunteers ranging in age from twenty-one to twenty-six years. All tests began in the early morning and ended in the afternoon. No subject was allowed to eat, smoke or drink stimulating beverages before or during the experiment.

Each of the 4 medications was presented to each subject on a separate day in the order prescribed by a Bugelski[5] Latin-square design. Each subject's test days were at least two days apart. Neither the subjects nor the observers knew which agent was being administered on any given day. Each drug was injected subcutaneously and in accord with body weight. The subjects received, per 70 kg. of body weight, 10 mg. of morphine, 30 mg. of dihydroisocodeine, 30 mg. of dihydrocodeine, or 1 ml. of physiologic saline solution as a placebo.

The measurements included blood pressure, heart rate, respiratory rate and minute-volume breathing. Blood-pressure recordings were taken with a sphygmomanometer. The pulse rate was counted over half a minute, and the respiratory rate over three minutes. For the minute-volume recording, a dry flow meter was used, through which the subjects inhaled room air or 5 per cent carbon dioxide in oxygen. Exhalation into the open was arranged through two low-resistance valves next to the subject's mouth. The mouthpieces used were those customarily employed in determinations of basal metabolism. Before every recording the subjects rested in a chair for thirty minutes. After every respiratory recording the subject walked for five minutes every hour. During the ventilation experiments the subject's nose was closed by a clamp. To approach a reasonable state of steadiness the subjects were required to breathe room air through the machine for five minutes before rate and volume were recorded for a three-minute period. For the determinations of 5 per cent carbon dioxide a period of nine minutes on carbon dioxide was required before recording was started. All recordings were made with the subjects in the sitting position.

TABLE 2. *Relief of Pain from Dihydrocodeine As Compared with Standard Dose of Morphine.*

NO. OF PATIENTS	DOSE OF DIHYDRO-CODEINE	RELIEF OBTAINED	DOSE OF MORPHINE	RELIEF OBTAINED	RELIEF OBTAINED WITH DIHYDRO-CODEINE MINUS MORPHINE
	mg.	%	*mg.*	%	%
21	15	56	10	89	−33
55	30	70	10	82	−12
15	45	50	10	63	−13

Before medication, two recordings were made with an interval of ten minutes between them. The mean values of these observations served as a base line against which changes after medication could be evaluated. The statistical analysis of these data is summarized in Table 6.

TABLE 3. *Comparison of Patients Reporting Good (More than 50 per Cent) vs. Poor (Less than 50 per Cent) Relief of Pain under Morphine, 10 Mg., and Dihydrocodeine, 30 Mg.*

			Severe Pain				Moderate Pain	
			Morphine, 10 mg.				Morphine, 10 mg.	
			Good relief	Poor relief			Good relief	Poor relief
45 min. after medication	Dihydrocodeine, 30 mg.	Good relief	17	2	Dihydrocodeine, 30 mg.	Good relief	17	3
		Poor relief	4	2		Poor relief	6	1
			Morphine, 10 mg.				Morphine, 10 mg.	
			Good relief	Poor relief			Good relief	Poor relief
90 min. after medication	Dihydrocodeine, 30 mg.	Good relief	17	3	Dihydrocodeine, 30 mg.	Good relief	23	2
		Poor relief	4	1		Poor relief	2	0

TABLE 4. *Comparison of Patients Reporting Complete (100 per Cent) vs. Incomplete (Less than 100 per cent) Relief of Pain under Morphine, 10 Mg., and Dihydrocodeine, 30 Mg.*

			Severe Pain				Moderate Pain	
			Morphine, 10 mg.				Morphine, 10 mg.	
			Complete relief	Incomplete relief			Complete relief	Incomplete relief
45 min. after medication	Dihydrocodeine, 30 mg.	Complete relief	3	1	Dihydrocodeine, 30 mg.	Complete relief	5	1
		Incomplete relief	4	17		Incomplete relief	8	13
			Morphine, 10 mg.				Morphine, 10 mg.	
			Complete relief	Incomplete relief			Complete relief	Incomplete relief
90 min. after medication	Dihydrocodeine, 30 mg.	Complete relief	4	0	Dihydrocodeine, 30 mg.	Complete relief	6	2
		Incompete relief	4	17		Incomplete relief	6	13

TABLE 5. *Frequency of Severe and Moderate Pain Occurring Early and Late Postoperatively.**

		12 to 24 hr. postoperatively		
		Severe pain	Moderate pain	
0-12 hr. postoperatively	Severe pain	46	26	$p<0.01$†
	Moderate pain	5	12	
		24-48 hr. postoperatively		
		Severe pain	Moderate pain	
0-24 hr. postoperatively	Severe pain	21	26	$p<0.01$†
	Moderate pain	3	12	

*Pain rated by patient before each medication; tables present only 1st pain rating obtained within specified intervals.
†For method of computation, see Mosteller.[4]

Subjective Side Effects

In addition to the physiologic measurements described above, psychologic measurements were carried out in the first group of 10 and in an additional group of 20 normal subjects. Two psychologic tests were used: a questionnaire and an adjective check list. These tests were designed to yield information concerning drug-induced effects on certain aspects of mood and subjective state. Both tests were given three times on each experimental day. Each subject took the tests twenty minutes before, one hour after and four hours after medication.

One of the tests was a 12-item rating-scale questionnaire, based on an earlier questionnaire developed by Lasagna, von Felsinger and Beecher.[6] Each of the 12 items on the questionnaire had a 7-point rating scale (-3, -2, -1, 0, $+1$, $+2$, $+3$) in which each of the extreme points of the scale (-3 and $+3$) were defined by opposite phrases or sentences. (With the simultaneous presentation of opposites the hazard of the leading question is minimized.) The subject's task was to choose, from the 7 points on the scale, the point most accurately corresponding to his current psychologic state. For example, the first item on the questionnaire is sleepy vs. awake. A rating of -3 means "I feel very, very sleepy"; a rating of $+3$ means "I feel completely awake"; and ratings -2, -1, 0, $+1$, and $+2$ refer to degrees of sleepiness falling between "very, very sleepy" and "completely

awake." The 12 items on the questionnaire are as follows:

1. Sleepy vs. awake.
2. Not peppy or energetic vs. peppy and energetic.
3. Mind seems slow, dull and sluggish vs. mind seems alert and active.
4. Groggy and confused vs. clearheaded.
5. Uneasy and afraid vs. safe, secure and unafraid.
6. Worried and troubled vs. not worried or troubled.
7. Restless, nervous and tense vs. calm, relaxed and serene.
8. Indifferent and unsympathetic vs. tolerant and considerate.
9. Grouchy and easily angered vs. good-natured and not easily angered.
10. Shy and not sure of self vs. self-confident and assured.
11. Sad and gloomy vs. happy and cheerful.
12. Dreamy with things seeming unusual and unreal vs. not dreamy and things not seeming unusual and unreal.*

TABLE 6. *Comparison of the Effect of Morphine, 10 Mg., Dihydroisocodeine, 30 Mg., Dihydrocodeine, 30 Mg., and Placebo on the Respiratory Minute Volume of 10 Normal Subjects.*

	MORPHINE VS. DIHYDROISOCODEINE	MORPHINE VS. DIHYDROCODEINE	MORPHINE VS. PLACEBO	DIHYDROISOCODEINE VS. DIHYDROCODEINE	DIHYDROISOCODEINE VS. PLACEBO	DIHYDROCODEINE VS. PLACEBO
With subject breathing 5% carbon dioxide:						
M_D*	+0.45	+2.53	+3.02	+2.08	+2.58	+0.50
S_D†	1.14	0.89	1.44	1.06	0.62	1.14
t‡	0.39	2.82	2.10	1.97	4.19	0.44
p§	>0.50	<0.02	<0.10	<0.10	<0.01	>0.50
With subject breathing room air:						
M_D*	+0.75	+1.70	+2.08	+0.95	+1.41	+0.38
S_D†	0.53	0.57	0.58	0.57	0.54	0.48
t‡	1.42	2.97	3.56	1.68	2.62	0.80
p§	<0.20	<0.02	<0.01	<0.20	<0.05	<0.50

*Difference between means measured in terms of liters per minute.
†Standard deviation of difference scores.
‡Correlated "t" value.
§Probability based on 2-tail test.

The second psychologic test used was a slight modification† of a 70-item adjective check list developed by Wendt, Nowlis and Nowlis[7] at the University of Rochester. When the subject takes this test he is instructed to rate the adjectives according to the degree to which they describe his present "feelings, state or mood." The adjective check list provides a measure of "dysphoria euphoria."

The data from another study in which the check list was used[8] have given us information concerning the degree to which college males like or dislike the feelings and moods described by each of the adjectives. On the basis of this information we were able, in the present study, to give each subject a score for "dysphoria-euphoria" each time the subject checked the list of adjectives.

*In this listing of the 12 items of the questionnaire, and in Tables 8-11, the undesirable state or characteristic is given first in an attempt to simplify discussion. However, in the experiment proper, half the undesirable items were presented first, and half were presented second, in random fashion.

†Eight new adjectives were added, and a "dysphoria-euphoria" measure was developed.

In developing the "dysphoria-euphoria" scale, we asked 22 subjects to rate each of the 78 adjectives on a 5-point scale, in terms of the degree to which they liked or disliked the feeling or mood described by the adjective. Certain adjectives (for example, nauseated, sad, genial and nervous) were either universally liked or universally disliked by all 22 subjects. Certain other adjectives (such as impulsive, lackadaisical, reckless, talkative and warm) were liked by some subjects and disliked by others. The 36 adjectives specified below were chosen to be used in our "dysphoria-euphoria" test because each satisfied two requirements: at least 20 of the 22 subjects agreed in rating the adjectives as being desirable or undesirable; and no more than 6 of the 22 subjects gave the adjective a neutral rating. Thus, the 36 adjectives that are used to evaluate "dysphoria-euphoria" were considered by most of the college males to be either definitely desirable or definitely undesirable. These 36 adjectives fall into the following 4 groups: very desirable — active, cheerful, effective, efficient, enthusiastic, genial, joyous and resourceful; mildly desirable — ambitious, industrious, kindly, original, peaceful, relaxed, satisfied, trustful, vigorous and witty; mildly undesirable — belligerent, itchy, nervous, sad, self-conscious, shy, sluggish, timid, weak and weary; and very undesirable — blue, brooding, dizzy, downhearted, headache (*sic*), jittery, nauseated and unhappy. The degree of desirability or undesirability of each adjective is taken into account in our scoring of a subject's adjective check list for "dysphoria-euphoria," — for example, checking a very undesirable adjective contributes more to the "dysphoria" score than checking a mildly undesirable adjective.

RESULTS

The usefulness of an analgesic agent depends upon the degree of pain relief, its duration of action and the type and severity of side effects, including addiction propensities. (The addiction problem is outside the scope of this study.)

Analgesia

The relative potency of morphine, dihydrocodeine and dihydroisocodeine have been compared in several studies in this laboratory during the past four years. Tables 3 and 4 show that when the pain level is controlled and correlated data are used, dihydrocodeine, 30 mg., is not significantly less potent than morphine, 10 mg., although there is a trend in favor of morphine (Table 2 presents these data in terms of percentage of relief). This finding is of particular interest in view of the remarkable "absence" of side effects in the 30-mg. dose of dihydrocodeine, as noted below. It will be shown that the effect of this agent is of somewhat shorter duration than that of morphine, but since the "new" agent has so few side effects it can be given again and the difference in duration of action is thus not of great practical importance.

The data in Table 4 indicate the frequency of relief at forty-five and ninety minutes after the administration of dihydrocodeine, 30 mg., or morphine, 10 mg., given for severe or moderate pain. In this table a strict criterion of complete relief (100 per cent) was used. In Table 3 a less severe criterion was applied to the same data: poor relief (less than 50 per cent) was compared with good relief (more than 50 per cent). The frequencies in Tables 3 and 4 were

then evaluated, by means of an exact binomial test. Morphine, 10 mg., is not more potent, to a statistically significant degree, than dihydrocodeine, 30 mg., except in the severe test condition of Table 4, in which complete relief is compared with incomplete relief. Here, in moderate pain, forty-five minutes after medication, morphine is significantly better than dihydrocodeine ($p<0.05$).

Decreasing this dose of dihydrocodeine to 15 mg. results in marked loss of analgesic power; increasing it to 45 mg. does not improve its performance in a small sample (Table 2).

In Table 1, Groups A and B are shown separately because of a time gap of three years between the studies. The close corroboration of the earlier experiment (first phase in Group A) by the recent study (second phase in Group B) confirms the reproducibility of the method, since different teams were used. Those who obtained the data in the second phase were not aware of the results obtained in the first.

Group C of Table 1 comprises Group A and Group B and indicates that dihydroisocodeine, 30 mg. and 60 mg., and morphine, 10 mg., do not differ from one another in analgesic potency. Dihydroisocodeine, 30 mg., produced side effects that were about as severe as those observed with 10 mg. of morphine and much more severe than those seen with 30 mg. of dihydrocodeine. An analysis of the 15-mg. dihydroisocodeine dose compared with 10 mg. of morphine shows this drug to be considerably weaker than morphine, 10 mg., in relieving severe pain, but equal to morphine in relieving moderate pain. Evaluation of the side effects of dihydroisocodeine, 15 mg., remains to be done.

It was of interest to see how the drugs investigated compared with morphine as a hypnotic. Evaluation of the collected data showed no difference in number of patients found asleep during the second through the sixth hour after medication. Relatively consistently it was observed that approximately 50 per cent of the patients were found asleep within this period, regardless of medication employed.

Duration of Action

The duration of action is defined as the time elapsing between two medications given against pain, on the basis of the patients' requests. Since all medications are given every two hours as necessary, the minimum duration of action cannot be less than two hours. Similarly, since the observation period is limited to six hours, this interval is the maximum a given medication can last. All doses yielding relief for more than six hours are recorded as giving only six hours of relief. This method of evaluation was found to be satisfactory for the drugs under investigation. If the data suggest that a drug offers relief of more than six hours' duration with apparent regularity, this can be demonstrated by comparison for "relief lasting six hours or more" between the drug and the standard. In the present study, morphine was not superior to the other agents in the frequency of "relief lasting six hours or more."

The mean duration of action as defined above for 10 mg. of morphine and 30 mg. of dihydrocodeine when given for severe pain was five and one-tenth hours and four and four-tenths hours, respectively. When the drugs were given for moderate pain the duration for morphine, 10 mg., and dihydrocodeine, 30 mg., was five and three-tenths and four and three-tenths hours. A "two-tail t test" for correlated data with 14 pairs of observations comparing the mean duration of action between morphine and dihydrocodeine gives a "t" of 2.00 ($p<0.1$) for severe pain and a "t" of 2.78 ($p<0.02$) for moderate pain.

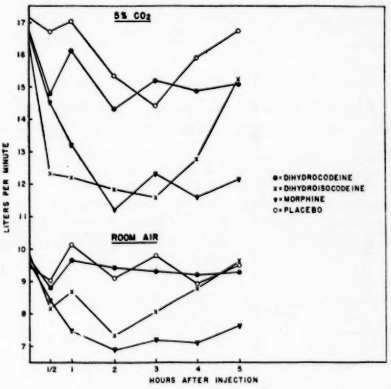

FIGURE 1. *Effect of Dihydrocodeine, Dihydroisocodeine, Morphine and Placebo on Minute-Volume Breathing of Room Air or 5 per Cent Carbon Dioxide (10 Subjects).*

Physical Side Effects

The physical side effects were studied in 10 normal volunteers. Figure 1 gives a graphic representation of the response curves for minute volume using room air or 5 per cent carbon dioxide. In the curves placebo, dihydrocodeine, 30 mg., dihydroisocodeine, 30 mg., and morphine, 10 mg., are shown to be increasingly depressant in the order listed. Drug differences in the over-all depression of minute volume were evaluated with the use of the "t" test for correlated data. The results are presented in Table 6. Dihydroisocodeine, 30 mg., was not found to be significantly different from morphine, 10 mg. However, dihydrocodeine was found to differ significantly from morphine. Although the difference between dihydroisocodeine and placebo was significant, the difference between dihydrocodeine and placebo was not statistically significant. These relations were true under both

conditions of respiratory measurement — room air and 5 per cent carbon dioxide.

TABLE 7. *Side Effects Mentioned Spontaneously by 30 Normal Subjects.*

SIDE EFFECT	PATIENTS ON DIHYDROISOCODEINE	PATIENTS ON DIHYDROCODEINE	PATIENTS ON MORPHINE	PATIENTS ON PHYSIOLOGIC SALINE SOLUTION
	30 mg.	*30 mg.*	*10 mg.*	
Nausea	7	0	10	0
Headache	0	0	0	1
Dizziness	3	0	7	0
Sleepiness	5	0	4	0
Pepped-up feeling	6	0	0	0
Shakiness	0	0	3	0
Sweating	1	0	3	0

All other physical measures, such as blood pressure, pulse and respiratory rates, yielded no significant changes attributable to medication, with one exception: in the carbon dioxide test dihydroisocodeine reduced respiratory rate significantly more than a placebo ($p<0.01$).

TABLE 8. *Significant Increases in Psychologic Side Effects Produced by Morphine, Dihydroisocodeine, Dihydrocodeine and Placebo One Hour after Medication.*

SUBJECT'S ASSESSMENT ON QUESTIONNAIRE ITEMS	SERIES	P VALUE WITH MORPHINE, 10 MG. ‡	P VALUE WITH DIHYDROISOCODEINE, 30 MG.‡	P VALUE WITH DIHYDROCODEINE, 30 MG.‡	P VALUE WITH PLACEBO‡
1. Sleepy	I*	+ 0.001	+ 0.05	#	#
	II†	+ 0.001	+ 0.01	#	#
2. Uneasy	I*	+ 0.10	#	#	#
	II†	#	#	#	#
3. Mind slow	I*	+ 0.01	+ 0.05	#	#
	II†	+ 0.001	+ 0.02	#	#
4. Dreamy	I*	+ 0.02	+ 0.05	#	#
	II†	+ 0.001	+ 0.001	#	#
5. Sad	I*	+ 0.10	#	#	− 0.10
	II†	#	#	#	#
6. Grouchy	I*	+ 0.05	#	#	#
	II†	#	#	#	#
7. Groggy	I*	+ 0.01	+ 0.05	#	#
	II†	+ 0.001	+ 0.01	#	#
8. Shy	I*	+ 0.10	#	#	#
	II†	#	#	#	#
9. No pep	I*	+ 0.01	+ 0.05	#	+ 0.10
	II†	+ 0.01	#	#	#
10. Worried	I*	#	#	#	#
	II†	#	#	− 0.05	#
11. Indifferent	I*	#	#	#	+ 0.05
	II†	#	#	#	+ 0.01
12. Restless	I*	#	#	#	#
	II†	#	#	#	#
Dysphoria	II†	+ 0.001	+ 0.05	#	#

*10 subjects.

†20 subjects.

‡+ and − signs indicate direction of change — i.e., increase or decrease in characteristic. Values to right of signs indicate level of significance of this difference. Thus, top + 0.001 in upper left cell means that in Series I subjects reported being more sleepy 1 hr. after receiving morphine, 10 mg., than 20 min. before receiving morphine & that this difference is significant at or beyond 0.001 level of confidence using two-tail "t" test. Symbol # indicates that difference does not reach 0.10 level of significance. Means, standard deviations, & "t" values not reported, to permit all data to be summarized in 1 table.

Twenty normal volunteers were added to the 10 referred to above for a more complete appraisal of the psychologic side effects presented below. Four of these 30 normal volunteers (as pointed out below) vomited under morphine; none vomited under the other medications. Table 7 gives a list of side effects reported spontaneously. It is interesting to observe the high frequency of spontaneously reported nausea under morphine and dihydroisocodeine and the absence of this response under placebo and dihydrocodeine.

TABLE 9. *Significant Increases in Psychologic Side Effects Produced by Morphine, Dihydroisocodeine, Dihydrocodeine and Placebo Four Hours after Medication.*

SUBJECT'S ASSESSMENT ON QUESTIONNAIRE ITEMS	SERIES	P VALUE WITH MORPHINE, 10 MG.‡	P VALUE WITH DIHYDROISOCODEINE, 30 MG.‡	P VALUE WITH DIHYDROCODEINE, 30 MG.‡	P VALUE WITH PLACEBO‡
1. Sleepy	I*	+ 0.10	+ 0.10	#	#
	II†	+ 0.05	#	#	#
2. Uneasy	I*	+ 0.02	#	#	#
	II†	#	#	#	− 0.10
3. Mind slow	I*	+ 0.01	#	#	#
	II†	+ 0.02	#	#	#
4. Dreamy	I*	+ 0.10	#	#	#
	II†	+ 0.01	+ 0.05	− 0.10	#
5. Sad	I*	+ 0.05	#	#	#
	II†	#	#	#	#
6. Grouchy	I*	+ 0.02	#	#	#
	II†	#	#	#	#
7. Groggy	I*	+ 0.10	#	#	#
	II†	+ 0.05	#	#	#
8. Shy	I*	+ 0.10	#	#	#
	II†	+ 0.001	#	#	#
9. No pep	I*	+ 0.01	#	#	#
	II†	+ 0.001	#	− 0.10	#
10. Worried	I*	+ 0.10	#	#	#
	II†	#	#	#	#
11. Indifferent	I*	#	#	#	#
	II†	#	#	#	#
12. Restless	I*	+ 0.02	#	#	#
	II†	#	#	#	#
Dysphoria	II†	+ 0.001	#	#	#

*10 subjects.

†20 subjects.

‡+ and − signs indicate direction of change — i.e., increase or decrease in characteristic. Values to right of signs indicate level of significance of this difference. Thus, top + 0.10 in upper left cell means that in Series I subjects reported being more sleepy 4 hr. after receiving morphine, 10 mg., than 20 min. before receiving morphine & that this difference is significant at or beyond 0.10 level of confidence using two-tail "t" test. Symbol # indicates that difference does not reach 0.10 level of significance. Means, standard deviations, & "t" values not reported, to permit all data to be summarized in 1 table.

Psychologic Side Effects

Considering the extensive psychologic effects of narcotics we believe it is important to give more emphasis to such effects of these agents than has been customary in the past. The psychologic effects were evaluated first in a group of 10 subjects and then in the additional group of 20 subjects, as mentioned above.

The data concerning drug-induced change in mood and subjective physical state are summarized in Tables 8-11. Each table has 13 rows of data. The first 12 rows indicate change in the 12 items of the questionnaire. The last row indicates change in "dysphoria-euphoria." Information contained in these tables can be summarized and amplified as follows:

Morphine (10 mg.) produces a greater number of significant subjective side effects than dihydrodeine (30 mg.) both produce a significant increase in dysphoria — highly significant with morphine.* With morphine the dysphoria is still present four hours after medication; however, with dihydroisocodeine the dysphoria has disappeared four hours after medication.

Agreement between results on Series I (with 10 subjects) and II (with 20 subjects) is quite high (Tables 8-11). Thus, the technics used to measure drug-induced change in mood and subjective physical state give reproducible results.

TABLE 10. *Significant Differential Psychologic Side Effects of Morphine (10 Mg.), Dihydroisocodeine (30 Mg.), Dihydrocodeine (30 Mg.) and Placebo One Hour after Medication.*

Subject's Assessment on Questionnaire Items	Series	P Value with Morphine vs. Dihydrocodeine‡	P Value with Dihydroisocodeine vs. Dihydrocodeine‡	P Value with Dihydrocodeine vs. Placebo‡	P Value with Morphine vs. Dihydroisocodeine‡	P Value with Dihydroisocodeine vs. Placebo‡	P Value with Morphine vs. Placebo‡
1. Sleepy	I*	+ 0.001	+ 0.02	#	#	+ 0.01	+ 0.01
	II†	+ 0.01	+ 0.02	#	#	+ 0.01	+ 0.01
2. Uneasy	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	#
3. Mind slow	I*	+ 0.01	+ 0.01	#	#	+ 0.05	+ 0.02
	II†	+ 0.01	+ 0.05	#	#	#	+ 0.02
4. Dreamy	I*	+ 0.05	+ 0.05	#	#	+ 0.10	+ 0.10
	II†	+ 0.01	+ 0.01	#	#	+ 0.01	+ 0.001
5. Sad	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	#
6. Grouchy	I*	+ 0.10	#	#	#	#	+ 0.10
	II†	#	#	#	#	#	#
7. Groggy	I*	+ 0.01	+ 0.02	#	#	+ 0.10	+ 0.05
	II†	+ 0.02	+ 0.05	#	#	+ 0.10	+ 0.01
8. Shy	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	#
9. No pep	I*	+ 0.01	+ 0.05	#	#	#	+ 0.02
	II†	+ 0.05	#	#	#	#	+ 0.01
10. Worried	I*	#	#	#	#	#	#
	II†	+ 0.05	+ 0.02	#	#	#	#
11. Indifferent	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	− 0.05
12. Restless	I*	#	#	#	+ 0.10	#	+ 0.10
	II†	#	#	#	#	#	#
Dysphoria	II†	+ 0.001	+ 0.02	#	#	+ 0.05	+ 0.02

*10 subjects.

†20 subjects.

‡+ sign means that relatively greater increase in characteristic occurred under 1st of 2 drugs being compared than under 2d. − sign means that relatively greater increase in characteristic occurred under 2d drug. Values to right of signs indicate level of significance of difference in amount of change under 2 drugs being compared. Symbol # indicates that difference does not reach 0.10 level of significance, using two-tail "t" test.

Morphine (10 mg.) produces a greater number of significant subjective side effects than dihydroisocodeine (30 mg.), dihydrocodeine (30 mg.) or placebo.

One hour after medication the dihydroisocodeine (30 mg.) side effects are almost as numerous and severe as those of morphine (10 mg.). However, four hours after medication the dihydroisocodeine side effects have almost disappeared whereas the morphine side effects still persist.

Dihydrocodeine (30 mg.) produces far fewer side effects than dihydroisocodeine (30 mg.) or morphine (10 mg.). Indeed, in the present study, 30 mg. of dihydrocodeine produces no more side effects than a placebo.

Dihydrocodeine (30 mg.) and a placebo do not produce significant change in "dysphoria-euphoria." Morphine (10 mg.) and dihydroisocodeine (30 mg.) both produce a significant increase in dysphoria — highly significant with morphine.* With morphine the dysphoria is still present four hours after medication; however, with dihydroisocodeine the dysphoria has disappeared four hours after medication.

Agreement between results on Series I (with 10 subjects) and II (with 20 subjects) is quite high (Tables 8-11). Thus, the technics used to measure drug-induced change in mood and subjective physical state give reproducible results.

Discussion

In the presentation of the results little detail was offered about dihydroisocodeine, 30 mg., which is approximately equal to 10 mg. of morphine in analgesic potency and side-effect liability. Attention is focused on dihydrocodeine, 30 mg., which is a useful analgesic and does not have the undesirable side effects of morphine. Although in our study morphine, 10 mg., showed a slightly greater degree of pain relief than dihydrocodeine, 30 mg., its superiority was not statisti-

*The fact that morphine produced dysphoria rather than euphoria in the present experiment supports an earlier finding by Lasagna, von Felsinger and Beecher[4] using different technics and different subjects.

cally significant. A large series would be required to differentiate the comparative effectiveness of these two drugs.

We do not wish to give the impression that dihydrocodeine, 30 mg., produces absolutely no side effects. Our point is that dihydrocodeine, 30 mg., does not produce the classic side effects evoked to a very significant degree by both morphine, 10 mg., and dihydroisocodeine, 30 mg. — that is, respiratory depression, sleepiness, mental confusion, sluggishness, loss of "energy," dysphoria and nausea.

It was pointed out that dihydrocodeine, 30 mg., may be a weaker analgesic than morphine, 10 mg. Table 2 shows a 12 per cent difference. Table 4, applying a very stringent criterion (complete relief), shows morphine to be consistently better than dihydrocodeine (when the lower left cell is compared with upper right cell for every condition). In the statistical analysis, these were the cells used. However, it should not be overlooked that the upper left and lower right cells offer important information. They give the incidence where morphine and dihydrocodeine did *not* differ. Thus Table 4 shows the largest numbers in the lower right cells (incomplete relief with both morphine and dihydrocodeine), and Table 3 shows the largest numbers in the upper left cells (*good* relief for both morphine and dihydrocodeine). It therefore appears that in most patients dihydrocodeine is as good as morphine; where dihydrocodeine and morphine differ, morphine is usually stronger.

Lasagna and Beecher[9] demonstrated codeine phosphate, 60 mg. per 70 kg. of body weight, to be 11 per cent weaker in analgesic power than 10 mg. of morphine. This compares well with a 12 per cent difference between dihydrocodeine and morphine (Table 2) in the present study. However, respiratory depression and incidence of side effects are marked with 60 mg. of codeine and slight or absent with 30 mg. of dihydrocodeine.

Careful comparisons between dihydrocodeine and morphine in different dosages as well as comparisons between dihydrocodeine and other agents such as codeine are needed. In our hands dihydrocodeine, 30 mg., is a potent analgesic with few or no clinically important side effects and thus is an important candidate for extensive clinical trial. Higher dosages are presently being tested in this laboratory.

In a study by Himmelsbach,[10] who used dihydrocodeine as a substitute for morphine in addicts, a 3.5:1 ratio of dihydrocodeine to morphine was reported to be adequate. In the present study, where dihydrocodeine was substituted for morphine as an

TABLE 11. *Significant Differential Psychologic Side Effects of Morphine (10 Mg.), Dihydroisocodeine (30 Mg.), Dihydrocodeine (30 Mg.) and Placebo Four Hours after Medication.*

SUBJECT'S ASSESSMENT ON QUESTIONNAIRE ITEMS	SERIES	P VALUE WITH MORPHINE VS. DIHYDROCODEINE‡	P VALUE WITH DIHYDROISOCODEINE VS. DIHYDROCODEINE‡	P VALUE WITH DIHYDROCODEINE VS. PLACEBO‡	P VALUE WITH MORPHINE VS. DIHYDROISOCODEINE‡	P VALUE WITH DIHYDROISOCODEINE VS. PLACEBO‡	P VALUE WITH MORPHINE VS. PLACEBO‡
1. Sleepy	I*	+ 0.05	+ 0.05	− 0.10	#	#	#
	II†	+ 0.02	#	#	#	#	+ 0.02
2. Uneasy	I*	+ 0.05	#	#	+ 0.10	#	+ 0.05
	II†	#	#	#	#	#	#
3. Mind slow	I*	+ 0.01	#	#	#	#	+ 0.10
	II†	+ 0.02	#	#	#	#	+ 0.05
4. Dreamy	I*	+ 0.10	#	#	#	#	#
	II†	+ 0.01	+ 0.01	#	#	+ 0.02	+ 0.01
5. Sad	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	#
6. Grouchy	I*	+ 0.10	#	#	#	#	#
	II†	#	#	#	#	#	#
7. Groggy	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	+ 0.05
8. Shy	I*	#	#	#	#	#	#
	II†	+ 0.10	#	#	+ 0.10	#	+ 0.01
9. No pep	I*	+ 0.01	#	#	+ 0.10	#	+ 0.05
	II†	+ 0.001	#	#	+ 0.01	#	+ 0.01
10. Worried	I*	#	#	#	+ 0.10	#	+ 0.10
	II†	#	#	#	#	#	+ 0.10
11. Indifferent	I*	#	#	#	#	#	#
	II†	#	#	#	#	#	− 0.10
12. Restless	I*	#	#	#	+ 0.10	#	#
	II†	#	#	#	#	#	#
Dysphoria	II†	+ 0.001	#	#	+ 0.01	#	+ 0.05

*10 subjects.

†20 subjects.

‡+ sign means that relatively greater increase in characteristic occurred under 1st of 2 drugs being compared than under 2d. − sign means that relatively greater increase in characteristic occurred under 2d drug. Values to right of signs indicate level of significance of difference in amount of change under 2 drugs being compared. Symbol # indicates that difference does not reach 0.10 level of significance, using two-tail "t" test.

analgesic, the ratio of 3:1 was found to be optimal. Thus, good correlation exists between these independent studies using different methods of arriving at comparable doses of morphine and dihydrocodeine.

Finally, it should again be pointed out that postoperative wound pain changes in severity within the first postoperative day (Table 5). For the clinical evaluation of analgesics using postoperative wound pain this is of importance, because the performance of an analgesic will obviously be judged differently whether the drug is employed during the first twelve to twenty-four postoperative hours or thereafter. The division of the patients according to degree of pain (severe vs. moderate) immediately before medication can help to avoid errors in the evaluation of experimental drugs.

Summary

The analgesic power and side effects of dihydrocodeine and dihydroisocodeine were studied in man with postoperative wound pain. These drugs were compared with morphine as a standard. In the evaluation of side effects, morphine and placebo comparisons were made with the "new" agents in normal volunteers.

The outstanding result of this study was the finding that 30 mg. of dihydrocodeine per 70 kg. of body weight is a powerful analgesic agent, although somewhat less powerful than morphine, yet essentially free of both objective (for example, respiratory depression) and subjective (for example, nausea and mood changes) side effects. It is of somewhat shorter duration of action than 10 mg. of morphine. It is pointed out, however, that this limitation is not of practical importance since the agent has so few and such slight side effects that it can be readministered.

Dihydroisocodeine, 30 mg., is about as potent as morphine, 10 mg., in both analgesic effect and side-effect liability.

This study presents a further development in technics of appraisal of analgesic power, with emphasis here on two levels of pain and improved measurement of duration of effectiveness of the agents used. In addition to improvements in these directions we have attempted to present a more precise evaluation of the psychologic effects of the agents studied than has heretofore been carried out for this class of agents; such work represents a continuing major aim of this laboratory.

We are indebted to Professor Hugo Muench for statistical assistance and to Dr. Donald P. Pederson for his help on collecting some of the data on this study.

It was at the suggestion of Dr. Nathan B. Eddy that we studied these drugs. The dihydrocodeine was provided through the courtesy of the Bilhuber-Knoll Corporation, and the dihydroisocodeine through the courtesy of the New York Quinine and Chemical Works.

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INCIDENCE OF MEGALOBLASTIC ANEMIA AFTER TOTAL GASTRECTOMY*

Lloyd D. MacLean, M.D.,† and R. Dorothy Sundberg, Ph.D., M.D.‡

MINNEAPOLIS

THE investigations of Castle and co-workers[1-6] over the past quarter century strongly support the thesis that pernicious anemia is the result of a gastric defect manifested by an inadequate production of intrinsic factor, which is responsible for absorption of extrinsic factor, or vitamin B_{12}, from the gastrointestinal tract. If pernicious anemia is not a more complex deficit than a lack of intrinsic factor and if the stomach is the only source of this material, one would expect pernicious anemia to develop invariably after total gastrectomy. Studies utilizing the fecal or urinary excretion of radioactive vitamin B_{12} as an assay of intrinsic factor in the gastrointestinal tract reveal a failure of absorption of the vitamin in patients after total gastrectomy, as in persons with pernicious anemia.[2,3-5] Fox and Castle[6] had previously shown that tissue obtained from the body and fundus of normal human stomachs at autopsy contained highly active intrinsic factor. In contrast, the antrum was at best weakly active. Paulson et al.[7] found no intrinsic factor in duodenal juice obtained from patients after total gastrectomy. These investigations suggested that the site of intrinsic-factor production corresponds to the

*From the departments of Surgery and Anatomy and Laboratory Medicine, University of Minnesota Medical School.
Supported by United States Public Health Service Grant No. A-820.
†Research assistant, Department of Surgery, University of Minnesota Medical School.

‡Assistant professor of anatomy, University of Minnesota Medical School; hematologist, University of Minnesota Hospital Laboratory.

location of the gastric lesion in pernicious anemia — that is, the gastric body and fundus, as suggested by Magnus and Ungley.[8] More recent studies have detected intrinsic-factor activity in desiccated preparations of normal human duodenum; however, the possibility of passive adsorption or active absorption by this tissue was not excluded.[9]

form of liver extract or vitamin B_{12} may be administered.

Investigations with cobalt^{60}-labeled vitamin B_{12} suggest that pernicious anemia should occur regularly after total gastrectomy. However, Wintrobe[10] points out that there are very few if any authenticated cases on record.

TABLE 1. *Possible Cases of Megaloblastic Anemia after Total Gastrectomy Reported in the Literature (to 1954).*

SOURCE OF DATA	YEAR	INTERVAL AFTER SURGERY	BLOOD & BONE MARROW	COMMENT
		yr.		
Moynihan[16]	1911	3 2/3	Severe anemia	No recurrent carcinoma found
Hartman[17]	1921	2	Anemia, with high color index	—
Denig[18]	1929	8	Hemoglobin, 35%; high color index; nucleated red cells.	Gastrectomy for ulcer; myelitis; partial response to liver before death.
Hochrein[19]	1929	8	Hemoglobin, 54%; red-cell count, 1,500,000 (color index 1.7); megaloblasts in bone marrow.	Glossitis; lemon-yellow skin; diminished reflexes in ankles and knees.
Breitenbach[20]	1929		—	Somewhat doubtful case
Poole & Foster[21]	1931	3	Hemoglobin, 20%; red-cell count, 500,000.	No free hydrochloric acid before surgery; good response to liver.
Ungley[22]	1932	5/12	Macrocytic anemia with megaloblasts & macronormoblasts in blood & hypersegmented neutrophils	Marked improvement after liver by mouth
Meyer et al.[23]	1941	5	Megaloblastic anemia	Reticulocyte response to liver-extract therapy: anemia cured.
Weir[24]	1946	8	Macrocytic anemia; not megaloblastic bone marrow.	Patient producing free hydrochloric acid before gastrectomy
Morgans et al.[25]	1947	3	Hemoglobin, 72%; red-cell count, 3,280,000; mean corpuscular volume, 100.6 cu. microns; white-cell count, 4500; megaloblastic bone marrow.	Bone marrow reverted to normoblastic on folic acid in 2 wk.; no aggravation of neurologic component: liver therapy alone used thereafter.
MacDonald et al.[26] (2 patients)	1947	2 5	Severe macrocytic anemia	Investigators learned of 5 other cases in which macrocytic or megaloblastic anemia developed 4 to 8 yr. after total gastrectomy; 4 responded to liver; 1 responded to folic acid.
Beebe & Meneely[27]	1949	7	Macrocytic anemia	Patient had syphilitic gastritis; anemia & neurologic deficit responded to parenteral liver therapy.
Paulson et al.[7]	1950	7	Megaloblastic anemia	—
Conway & Conway[28]	1951	6	Typical megaloblastic bone marrow of pernicious anemia	Response to vitamin B_{12} alone suboptimal; anemia corrected by addition of folic acid.
Reimer[29] (6 patients)	1952	4-5	—	High incidence of macrocytic and megaloblastic anemia
Halsted et al.[2]	1954	6	Severe macrocytic anemia	34% reticulocytes on 6th day after parenteral administration of vitamin B_{12}
Tomada[30] (5 patients)	1954	7-8	Hyperchromic macrocytic anemia; megaloblastic bone marrow.	Pernicious anemia rare in Japan but common after gastrectomy

In the light of this evidence the infrequent occurrence of pernicious anemia after total gastrectomy may be the result of one or a combination of the following: an extragastric source of intrinsic factor exists in the human being; pernicious anemia is a more complex deficit than a simple lack of intrinsic factor; patients on whom total gastrectomy is performed usually have advanced carcinoma, and the survival period after operation may not be sufficiently long to allow the development of pernicious anemia; a complete removal of all gastric mucosa may not be accomplished in many gastrectomies believed to be total; and hematopoietically active substances such as folic acid may be ingested, or parenteral therapy in the

The present investigation was conducted to determine if pernicious anemia is inevitable after microscopically proved total gastrectomy and the time of its occurrence by a careful follow-up study of patients who underwent total gastrectomy at the University of Minnesota Hospitals up to June, 1954. With the exception of a patient who had previously had pernicious anemia, this disease did not begin until approximately three years or longer after operation. This investigation is concerned with the incidence of pernicious anemia among 13 patients who underwent total gastrectomy at the University of Minnesota Hospitals and survived for three years or longer, with data on prophylactic treatment, nutrition, splenectomy,

hematologic findings, free acid before operation and type of alimentary reconstruction. It has been possible to examine and obtain these data on all these patients. In addition, a report on 4 cases in which megaloblastic anemia followed total gastrectomy performed at the Minneapolis Veterans Administration Hospital is included.*

Review of the Literature

The first investigation of possible blood abnormality after extensive gastrectomy was made by Deganello[11] in 1900 on a patient who had undergone "near-total" gastrectomy for diffuse gastric carcinoma three months previously. The hemoglobin was 65 per cent (Sahli), and the red-cell count 3,670,000. The first successful total gastrectomy on a human patient was performed by Schlatter[12] in 1897. This patient was investigated by Hofmann[13] three months later, but no mention of a blood examination was made. That the stomach might be in some way related to pernicious anemia was suggested by Austin Flint.[14] The invariable presence of achlorhydria in pernicious anemia was well established by 1900.[15] The possibility that acid gastric secretions were necessary to prevent the intestinal overgrowth of bacteria that produced toxins causing pernicious anemia was also a prominent theory at the turn of the century. For these reasons clinicians must have considered the development of pernicious anemia a distinct possibility after total gastrectomy. The cases of possible megaloblastic anemia after total gastrectomy reported in the literature to 1954 are summarized in Table 1.

This review of the literature suggests that if a patient lives long enough after total gastrectomy, an anemia indistinguishable from a pernicious anemia will occur; however, the true incidence of the disease after total gastrectomy has never been established. Many of the reported cases may be a coincidental occurrence since gastric carcinoma is found more frequently in patients with pernicious anemia. Very little information is available on the production of free hydrochloric acid before operation in the reported cases. Another objection to concluding that pernicious anemia will inevitably occur after total gastrectomy is that little information is available concerning untreated patients who survive for long periods without the development of pernicious anemia. That such cases do exist up to eight years after gastrectomy has been reported.[26] In all groups microscopical proof that a total gastrectomy was performed is necessary. Information that the patient did not receive prophylactic therapy in the form of folic acid by mouth or liver extract or vitamin B_{12} parenterally is also essential. In addition, in many of the reported cases of pernicious anemia after total gastrectomy, the hematologic evidence is incomplete.

*Reported with the kind permission of Dr. Donald Ferguson, chief, Department of Surgery, Minneapolis Veterans Administration Hospital.

Some opinions that pernicious anemia is not inevitable after total gastrectomy are of interest. Pack and McNeer,[31] in a review of the world's literature on total gastrectomy for cancer, concluded that macrocytic anemia was a rare complication; however, long-term survival was also exceptional. Illingworth[32] believed that intrinsic factor is probably secreted by the jejunum and accounts for the few cases of pernicious anemia after total gastrectomy. Hall[33] stated that, since total gastrectomy rarely results in the development of megaloblastic anemia, the duodenum is probably a source of intrinsic factor. Paulson,[7] who reported 1 case of pernicious anemia after total gastrectomy, considered its occurrence to be extremely rare. In the experience of Farris, Ransom and Coller[34] this complication was rarely, if ever, encountered after total gastrectomy. Finally, it has been impossible to induce such an anemia in laboratory animals (dogs, monkeys, rats and cats) by total gastrectomy even though this has been attempted by many[35,36] and observation of dogs has been continued for as long as twelve years after gastrectomy.[37,38]

The following information was obtained on all patients in the present investigation: microscopical proof of total gastrectomy — that is, esophageal mucosa at the proximal line of the resected specimen and duodenum at the distal line of resection; absolute data on previous parenteral therapy with vitamin B_{12} and liver extract or folic acid by mouth; bone-marrow examination in all cases but 1 diagnosed as pernicious anemia; and knowledge of the free gastric acid before operation. The pertinent aspects of the case histories of these patients are included in the following section and are summarized in Table 2.

Case Reports

Case 1. J.K. (U.M.H. 709348), a 59-year-old man, was first seen at the University Hospitals in June, 1941. A diagnosis of adenocarcinoma of the stomach was established, and total gastrectomy and splenectomy were performed on July 2. He had no free gastric acid on analysis with histamine before operation. Intestinal continuity was re-established by means of loop esophagojejunostomy with enterostomy. Pathological examination of the specimen confirmed the diagnosis of adenocarcinoma of the stomach.

The patient was quite well until 1946, when he returned with anemia. Examination of the blood showed a hemoglobin of 9.5 gm. per 100 ml., a red-cell count of 2,700,000 and a hematocrit of 30 per cent. Megaloblastic bone marrow was observed. The mean corpuscular diameter was 9.0 microns, mean corpuscular volume 145 cu. microns, the mean corpuscular hemoglobin 44.1 micromicrogm., and mean corpuscular hemoglobin concentration 30.5 per cent. He responded to folic acid and liver therapy but voluntarily stopped this treatment in 1947 or 1948. A bone-marrow examination on May 1, 1950, revealed early megaloblastosis. He has remained on parenteral liver-extract therapy since that time and has maintained a normal hemoglobin.

Case 2. J. N. (U.M.H. 739722), a 63-year-old man, underwent total gastrectomy on April 13, 1944, for a perforating ulcer on the high, posterior portion of the stomach that proved to be benign on pathological examination. A loop esophagojejunostomy and enteroenterostomy was performed. The patient did not have free hydrochloric acid on gastric analysis with histamine before operation. He was started on prophylactic parenteral liver-extract therapy in 1945 and

had continued it regularly since that time. His weight was 77.1 kg. (170 pounds) before his illness and 63.5 kg. (140 pounds) immediately after operation and at present is 64.4 kg. (142 pounds); his ideal weight is 65.8 to 68.0 kg. (145 to 150 pounds). The hemoglobin was 14.7 gm. per 100 ml. in October, 1954.

CASE 3. J.E., (U.M.H. 746739), a 69-year-old man, underwent total gastrectomy for a diffuse scirrhous carcinoma of the stomach on August 15, 1944. A loop esophagojejunostomy with enteroenterostomy was utilized to restore alimentary continuity. He did not have free gastric acid on analysis with histamine before operation. He was readmitted to the hospital in April, 1947 (2 years and 8 months after operation), with a hemoglobin of 5.7 gm. per 100 ml., a red-cell count of 1,300,000, and a white-cell count of 4000. In the peripheral blood there were 3 nucleated red cells per 100 leukocytes. The bone marrow was megaloblastic, and no tumor cells were seen. The patient responded to parenteral liver-extract therapy and was also given 2 blood transfusions because of his emaciated condition. Liver function at this time was normal. Examination of an axillary lymph node showed no metastasis.

This patient weighed 54.4 to 56.7 kg. (120 to 125 pounds) before the onset of illness and over the year after total gastrectomy regained this weight. Before the last admission he lost 11.3 kg. (25 pounds); he died of metastatic carcinoma on May 20, 1947.

CASE 4. W.H. (U.M.H. 821236), a 65-year-old man, underwent total gastrectomy on January 15, 1947, for adenocarcinoma of the stomach, with reconstruction of the alimentary canal by means of esophagojejunostomy and enteroenterostomy. His usual weight before operation when he was well was 77.1 to 81.6 kg. (170-180 pounds); postoperatively, he weighed 52.1 to 54.4 kg. (115 to 120 pounds). In January, 1950, he noted weakness, fatigability and neurologic signs of subacute combined degeneration of the spinal cord. He had not received prophylactic therapy for pernicious anemia since operation. On June 27, 1950, the hemoglobin was 6.6 gm. per 100 ml., and the mean corpuscular diameter 8.5 microns; examination of the bone marrow revealed megaloblastosis. He responded to liver therapy with a 16.2 per cent reticulocyte response. He was well, with a normal hemoglobin, when last seen in January, 1955.

CASE 5. G.K. (U.M.H. 780144), a 66-year-old man, underwent total gastrectomy for benign gastric ulcer believed to be a cancer on September 17, 1947. Reconstruction of the alimentary canal was accomplished by means of esophagojejunostomy and enteroenterostomy. Free hydrochloric acid of 13° was observed without histamine before operation. He was capable of eating between two thirds and three quarters of his usual food intake in the early postoperative period. His normal weight was 72.6 kg. (160 pounds) before and 60.3 kg. (133 pounds) after operation.

TABLE 2. *Clinical Data on Total Gastrectomy at University of Minnesota Hospitals and Minneapolis Veterans Administration Hospital.*

CASE NO.*	AGE	DIAGNOSIS	FREE GASTRIC ACID BEFORE OPERATION	PROPHYLACTIC THERAPY	BONE MARROW	INTERVAL AFTER OPERATION	HEMOGLOBIN AT TIME OF BONE-MARROW BIOPSY	MEAN CORPUSCULAR DIAMETER	TYPE OF ALIMENTARY RECONSTRUCTION	SPLENECTOMY
	yr.					*yr.*	*gm./100 ml.*	*microns*		
1	59	Adenocarcinoma of stomach	0°	None before 1946	Megaloblastic	5 - 2/12	9.5	9.0	Esophagojejunostomy	Yes
2	63	Benign gastric ulcer	0°	Liver extract	——	——	14.7	—	Esophagojejunostomy	No
3	69	Adenocarcinoma of stomach	0°	None	Megaloblastic	2 - 8/12	5.7	—	Esophagojejunostomy	No
4	65	Adenocarcinoma of stomach	—	None	Megaloblastic	3 - 5/12	6.6	8.5	Esophagojejunostomy	No
5	66	Benign gastric ulcer	13°	None	Megaloblastic	2 - 8/12	13.3	8.3	Esophagojejunostomy	No
6	24	Esophageal varices	72°	None	Megaloblastic	7 - 5/12	9.0	10.0	Esophagojejunostomy	Yes
7	55	Adenocarcinoma of stomach	0°	Liver extract; folic acid.	——	——	14.0	—	Esophagojejunostomy	Yes
8	66	Adenocarcinoma of stomach	31°	None	Megaloblastic	3 - 11/12	12.7	8.7	Esophagoduodenostomy	Yes
9	74	Adenocarcinoma of stomach	0°	None	Megaloblastosis (early)	3 - 10/12	14.0	8.5	Roux-Y anastomosis	Yes
10	81	Adenocarcinoma of stomach	0°	None	Megaloblastic	3 - 3/12	9.7	8.9	Roux-Y anastomosis	Yes
11	74	Benign gastric ulcer	76°	None	Megaloblastic	3 - 3/12	14.4	8.5	Esophagojejunostomy	No
12	60	Gastric polyps	0°	None	Megaloblastosis (early)	3	12.2	8.5	Esophagoduodenostomy	No
13	64	Adenocarcinoma of stomach	0°	None	Typical post-splenectomy	2 - 5/12	13.6	8.0	Roux-Y anastomosis	Yes
14	26	Hypertrophic gastritis	0°	None	Megaloblastic	5 - 6/12	5.0	8.2	Esophagojejunostomy	No
15	66	Adenocarcinoma of stomach	0°	None	Megaloblastic	5 - 6/12	7.4	—	Esophagojejunostomy	No
16	43	Adenocarcinoma of stomach	0°	None	Megaloblasts in blood smear	4	10.4	9.6	Esophagojejunostomy	No
17	63	Cardiospasm & esophagitis	Present	None	Megaloblastic	3 - 11/12	8.7	7.8	Roux-Y anastomosis	No

*Cases 1-13, inclusive, operated on at University of Minnesota Hospitals, & cases 14-17, inclusive, at Minneapolis Veterans Administration Hospital.

He did not receive prophylactic therapy for pernicious anemia, and a bone-marrow biopsy 2 years and 8 months after total gastrectomy revealed megaloblastosis. At that time the hemoglobin was 13.3 gm. per 100 ml., the mean corpuscular diameter 8.3 microns, the mean corpuscular volume 106 cubic microns, the mean corpuscular hemoglobin 38.7 micromicrogm., and the mean corpuscular hemoglobin concentration 36.4 per cent. The patient died on June 4, 1951, of heart disease. Post-mortem examination was not performed.

CASE 6. C.G. (U.M.H. 764840), a 16-year-old boy, underwent total gastrectomy on July 7, 1947, for portal hypertension with bleeding esophageal varices. Analysis without histamine before operation revealed free gastric acid of 72°. Reconstruction of the intestinal tract was by loop esophagojejunostomy with enteroenterostomy. The patient has done quite well since operation and is at present a senior in dental school. He is able to ingest a normal meal and weighs 77.6 kg. (171 pounds) at present. His ideal weight is approximately 79.4 kg. (175 pounds). He did not receive prophylactic therapy for pernicious anemia after total gastrectomy. Bone-marrow examination on December 12, 1954, revealed megaloblastosis, whereas the bone marrow before operation had been normoblastic. The hemoglobin at the time of bone-marrow examination in 1954 was 9.0 gm. per 100 ml., and the mean corpuscular diameter 10 microns. There was a 16 per cent reticulocyte response to parenteral vitamin B_{12} therapy. The hemoglobin has remained normal since that time.

CASE 7. A.R. (U.M.H. 783264), a 55-year-old housewife, underwent total gastrectomy on November 13, 1947, for carcinoma of the gastric fundus. The intestinal tract was re-established by loop esophagojejunostomy. Pathological examination revealed a scirrhous carcinoma. The patient did not have free hydrochloric acid with histamine stimulation before operation. Prophylactic therapy with liver extract and folic acid was started in 1949, and she was well, without evidence of anemia, when last communicated with in January, 1955. She did not have a bone-marrow examination at that time. Her usual weight when she was well was 63.5 to 68.0 kg. (140 to 150 pounds), and her ideal weight 61.2 kg. (135 pounds); her present weight is 50.8 kg. (112 pounds).

CASE 8. P.M. (U.M.H. 823885), a 66-year-old man, underwent total gastrectomy and splenectomy on October 23, 1950, for adenocarcinoma of the stomach. Gastric analysis with histamine before operation revealed 31° of free hydrochloric acid. Gastrointestinal reconstruction was accomplished by esophagoduodenostomy. Esophagoscopy on September 5, 1951, revealed Grade 2 esophagitis, which did not prevent the patient from taking an adequate diet ranging between 2500 and 3200 calories during a controlled study period in the hospital. His weight in September, 1954, was 74.0 kg. (163 pounds); his usual weight before operation when he was well was 88.5 kg. (195 pounds), and his ideal weight 76.2 to 78.9 kg. (168 to 174 pounds). Bone-marrow examination 4 years after total gastrectomy revealed megaloblastosis. The hemoglobin at that time was 12.7 gm. per 100 ml., the red-cell count 3,690,000, the mean corpuscular volume 115 cubic microns, the mean corpuscular hemoglobin 34 micromicrogm., the mean corpuscular hemoglobin concentration 29.5 per cent, and the mean corpuscular diameter 8.7 microns. The white-cell count was 5400, and the peripheral blood revealed normoblasts and numerous Jolly bodies; the neutrophils were hyperlobulated. The patient has been given vitamin B_{12} since October, 1954, and is at present working actively as a farmer at the age of 71.

CASE 9. S.H. (U.M.H. 824423), a 70-year-old man, was admitted to the University Hospitals, and a total gastrectomy and splenectomy performed for adenocarcinoma of the stomach on November 10, 1950. The alimentary canal was re-established by means of a Roux-Y anastomosis. Histamine stimulation before operation showed achlorhydria. The patient weighed 77.1 kg. (170 pounds) when well before operation and 76.2 kg. (168 pounds) 3 years later. He was able to eat as much as before operation. Bone-marrow examination 3 years and 10 months after total gastrectomy revealed an early megaloblastosis. At that time the hemoglobin was 14.0 gm. per 100 ml., and the mean corpuscular diameter 8.5 microns.

CASE 10. E.L. (U.M.H. 832524), an 81-year-old man, underwent total gastrectomy for adenocarcinoma of the stomach on June 4, 1951. Reconstruction was accomplished by Roux-Y anastomosis. He did not have free gastric acid on analysis with histamine stimulation before operation. Despite his age he made an excellent recovery and has been very active since. Esophagoscopy on June 12, 1953, was negative. He was able to eat 85 per cent of the amount of food taken before operation. His usual preoperative weight was 59.0 kg. (130 pounds); his present weight is 54.9 kg. (121 pounds), and his ideal weight 63.5 kg. (140 pounds). He did not receive prophylactic therapy for pernicious anemia after the total gastrectomy. Bone-marrow examination on September 3, 1954, revealed megaloblastosis. The hemoglobin was 9.7 gm. per 100 ml., the hematocrit 29.8 per cent, and the mean corpuscular diameter 8.9 microns. Vitamin B_{12} therapy was started in February, 1955.

CASE 11. A.M., a 74-year-old man, underwent total gastrectomy for benign gastric ulcer on July 19, 1951. The preoperative free gastric acid with histamine stimulation was 76°. Reconstruction of the alimentary canal was done by means of loop esophagojejunostomy with enteroenterostomy. His weight was 65.8 kg. (145 pounds); his present weight is 60.3 kg. (133 pounds), and his ideal weight 63.5 kg. (140 pounds). He is working actively as a farmer and was urged to return for hematologic study 3 years and 3 months after operation, when a megaloblastic bone-marrow, hyperlobulated neutrophils and a hemoglobin of 14.4 gm. per 100 ml. were observed. He is now receiving parenteral vitamin B_{12} therapy.

CASE 12. (U.M.H. 837515), a 60-year-old farmer, underwent total gastrectomy for multiple gastric polyps on October 26, 1951. An esophagoduodenostomy was utilized to re-establish intestinal continuity. He was achlorhydric with histamine stimulation before operation. His usual preoperative weight was 83.9 to 86.2 kg. (185 to 190 pounds), and his weight 3 years postoperatively was 63.5 kg. (140 pounds). He works actively as a farmer. Bone-marrow biopsy on October 13, 1954, revealed early megaloblastosis. The hemoglobin was 12.2 gm. per 100 ml. at that time, and the mean corpuscular diameter 8.5 microns.

CASE 13. G. KV. (U.M.H. 838037), a 64-year-old deaf mute, underwent total gastrectomy on November 13, 1951, for scirrhous carcinoma of the stomach. A Roux-Y type of reconstruction was performed. He had no free acid on gastric analysis with histamine stimulation before the operation. His usual weight was 59.0 kg. (130 pounds); after recovery from the operation he weighed 52.1 kg. (115 pounds). Esophagoscopy on June 17, 1952, revealed minimal esophagitis. Bone-marrow biopsy 2 years and 5 months after total gastrectomy gave no evidence of megaloblastic anemia. The hematologic picture, including a mean corpuscular diameter of 8.0 microns and Jolly bodies, was consistent with previous splenectomy. The patient died on January 10, 1955; no post-mortem examination was performed.

The 4 patients described below underwent total gastrectomy at the Minneapolis Veterans Administration Hospital. All had microscopically proved total gastrectomy, and none had received treatment before the development of pernicious anemia. These are the only patients at this institution in whom megaloblastic anemia is known to have followed total gastrectomy. In all 4 patients the onset was three years or longer after the procedure. A complete follow-up study of all patients who underwent total gastrectomy at this institution was not possible; hence, no such determination of the incidence after total gastrectomy as was

possible with the University of Minnesota Hospitals patients can be made.

CASE 14. L.M. (M.V.A.H. 157180), a 26-year-old housewife, was suspected of having a peptic ulcer in 1945, and a gastrointestinal x-ray examination revealed a diffuse lesion that was thought to represent a lymphoblastoma of the stomach. She had no free hydrochloric acid on gastric analysis with histamine stimulation. Laparotomy and biopsy revealed only hypertrophic gastritis. The symptoms of nausea and vomiting continued, and a total gastrectomy was performed on May 6, 1956. The pathological diagnosis was hypertrophic gastritis. The patient did not receive prophylactic therapy for pernicious anemia, and when seen three years and seven months after operation, she had a full-blown megaloblastic anemia, with a hemoglobin of 5 gm. per 100 ml. and a mean corpuscular diameter of 8.2 microns. She responded fully to parenteral administration of vitamin B_{12}, the bone marrow returning to normal less than 1 month after initiation of therapy. The maximum reticulocyte response was 18.5 per cent.

CASE 15. C.C. (M.V.A.H. 158682), a 66-year-old man, underwent total gastrectomy on April 28, 1948, for adenocarcinoma of the stomach. He did not have free hydrochloric acid on gastric analysis with histamine stimulation before operation. A megaloblastic anemia (hemoglobin of 7.4 gm. per 100 ml.) and neurologic signs of subacute combined degeneration of the spinal cord were observed 4 years and 6 months after gastrectomy. The patient responded completely to parenteral vitamin B_{12} therapy, with return of the hemoglobin to normal (13.0 gm. per 100 ml.), reversion of the bone marrow to normal in less than 1 month, a reticulocyte response of 11 per cent and disappearance of the neurologic signs and symptoms. No further reticulocyte response followed the addition of folic acid and iron therapy 6 weeks after vitamin B_{12} was started.

CASE 16. G.R. (M.V.A.H. 862005), a 43-year-old man, underwent total gastrectomy for adenocarcinoma of the stomach in March, 1947. His usual weight was 54.0 kg. (119 pounds) before and 49.9 kg. (110 pounds) after the operation. He did not receive prophylactic therapy for pernicious anemia; on March 24, 1953, he was admitted to the hospital with a hemoglobin of 10.4 gm. per 100 ml., a mean corpuscular volume of 193 cubic microns, a mean corpuscular hemoglobin concentration of 31 per cent and a mean corpuscular diameter of 9.6 microns. He refused bone-marrow biopsy, but megaloblasts were found in the peripheral blood smear. The hemoglobin returned to normal after vitamin B_{12} therapy.

CASE 17. H.L. (M.V.A.H. 151043), a 63-year-old farmer, suffered from epigastric distress in 1939, and a diagnosis of cardiospasm was made after x-ray examination. A plastic procedure of the esophagogastric junction was performed in 1945. He continued to have dysphagia, and gastric analysis revealed the presence of free hydrochloric acid. A Heineke–Mikulicz pyloroplasty was performed on January 7, 1949, with little relief of symptoms. Subsequently, he noted hematemesis of a mild degree. In April a subtotal gastric resection resulted in a subsequent weight gain and improvement of the dysphagia. In 1950 vomiting and upper gastrointestinal hemorrhage recurred. The remaining gastric pouch and lower esophagus were resected, with Roux-Y reconstruction, on March 17, 1950. The bone marrow at that time was normal. No prophylactic treatment for pernicious anemia was given, and the hemoglobin remained normal until February 24, 1954, when the hemoglobin was 8.7 gm. per 100 ml., the mean corpuscular diameter 7.8 microns, the mean corpuscular volume 122 cubic microns, and the mean corpuscular hemoglobin concentration 31.5 per cent; the bone marrow was megaloblastic. The patient responded to vitamin B_{12} therapy with an 18 per cent rise in reticulocytes. He has remained well on this therapy alone. He weighs 56.7 (125 pounds); his usual weight before operation was 70.3 kg. (155 pounds), and his lowest weight after operation 51.7 (114 pounds). His intake averages between 2000 and 2500 calories per day.

DISCUSSION

Frequency and Time of Occurrence of Megaloblastic Anemia

The patient who has had a total gastrectomy is of special interest in that normal physiology has been altered in such a manner as to elucidate the pathogenesis of pernicious anemia. In this regard, a megaloblastic anemia indistinguishable from pernicious anemia appears to be a late but inevitable sequela of total gastrectomy manifested first as a megaloblastic bone marrow and later as anemia. With 1 exception all patients (11 in number) who underwent proved total gastrectomy at the University of Minnesota Hospitals and who did not receive prophylactic therapy for pernicious anemia and survived for over three years had a megaloblastic bone marrow. The patient in whom megaloblastosis did not develop lived longer than three years after total gastrectomy but underwent hematologic examination two years and five months later; this patient subsequently died. In all patients at the Minneapolis Veterans Administration Hospital, 4 in number, in whom a megaloblastic anemia followed total gastrectomy three or more years elapsed before the anemia appeared. This occurred regardless of the type of enteric reconstruction, whether by Roux-Y anastomosis, esophagoduodenostomy or loop esophagojejunostomy with enteroenterostomy, making it unlikely that the anemia is in any way related to the anemia of blind intestinal loop or intestinal stricture. In addition, Doscherholmen and Hagen[39] have shown that although patients with megaloblastic anemia associated with blind intestinal loop do not absorb radioactive vitamin B_{12}, the addition of intrinsic factor does not accomplish absorption as it does after total gastrectomy.[4]

Free Gastric Acid before Operation

Free acid was noted before operation in the gastric secretion of 5 patients, thereby decreasing the likelihood that all patients in whom pernicious anemia develops after total gastrectomy would have had the disease with or without the operation. A comparative group of 4 patients who underwent total gastrectomy one to three years previously did not exhibit the megaloblastic changes in the bone marrow. The total gastrectomy in the 17 cases investigated was performed for adenocarcinoma of the stomach in 10, for benign gastric ulcer in 3 and for gastric polyps, cardiospasm and esophagitis, hypertrophic gastritis and portal hypertension with esophageal varices in 1 case each.

Site of Intrinsic-Factor Production

Extensive distal subtotal gastrectomy does not detectably alter the normal absorption of orally administered radioactive vitamin B_{12}.[40] An investigation of 3 patients with proximal subtotal gastrectomy with excision of the gastric body and fundus and esophago-

antrostomy revealed that they were unable to absorb orally administered cobalt^{60}-labeled vitamin B_{12} unless intrinsic factor was also added.[4] This corresponds to the findings observed in patients with pernicious anemia after total gastrectomy.[2-4] One patient who underwent esophagoantrostomy was producing free gastric acid before operation and at that time excreted in the urine a normal quantity of orally administered radioactive vitamin B_{12} under the conditions of the Schilling[41] test, indicating intrinsic-factor production immediately before the operation.[4] The ability of 6 of the patients described above to absorb orally administered radioactive vitamin B_{12} has been investigated. All 6 (Cases 8, 10, 11, 12, 13 and 16) failed to absorb detectable amounts of the vitamin but did so when intrinsic factor was added.[3,4] Esophageal mucosa and duodenal mucosa were demonstrated microscopically on the excised surgical specimen in all patients after total gastrectomy. This evidence favors the opinion that the site of intrinsic-factor production in the human being coincides with the area of pathologic change in the stomach in pernicious anemia, in the body and fundus, and that the human antrum is not of importance in the elaboration of intrinsic factor.

Response to Vitamin B_{12} or Purified Liver Extract Alone

Vitamin B_{12} or purified liver extract alone has been effective in accomplishing a complete and persistent remission. The addition of folic acid after response to vitamin B_{12} in 1 patient did not induce a further reticulocytosis. This is in contrast to the finding of Conway and Conway,[28] who reported complete remission only when folic acid was added to vitamin B_{12} therapy for megaloblastic anemia after total gastrectomy. In 2 patients (Cases 14 and 15) the bone marrow returned to normal from megaloblastic after less than a month of parenteral vitamin B_{12} therapy. The use of folic acid alone in the treatment of megaloblastic anemia after total gastrectomy, we believe, carries the risk of aggravating the neurologic component of the disease. Multivitamin compounds containing folic acid are hazardous for the same reason.

The panmyelopathy, including megaloblasts and the characteristic alterations in neutrophils and cells of the megakaryocytic series after total gastrectomy, is similar in all respects to that seen in pernicious anemia in relapse.[42]

Megaloblastic Anemia and Sprue after Gastrectomy

That the development of a megaloblastic anemia after total gastrectomy is due to sprue or a nutritional defect other than vitamin B_{12} deficiency seems unlikely for a number of reasons. In the first place vitamin B_{12} alone accomplished complete remission of the anemia in the cases reported whereas folic acid is a specific deficiency in sprue.[43] Secondly, although patients with the sprue syndrome do not absorb radioactive vitamin B_{12}, the addition of intrinsic factor has no effect,[44] in contrast to the situation in pernicious anemia. Diarrhea, per se, occasionally causes an abnormally high fecal excretion of orally administered cobalt^{60}-labeled vitamin B_{12}, presumably indicating an intrinsic-factor deficiency. This false result has not been noted with the urinary-excretion test of Schilling.[4] Patients who have had total gastrectomy do not absorb radioactive vitamin B_{12} unless supplied with intrinsic factor, indicating that this factor is not due merely to the diarrhea that commonly occurs in such cases. Thirdly, many of the patients described above were within 10 per cent of their ideal weights for age, height and body build, indicating nearly normal nutrition. Finally, nutritional macrocytic anemia is not associated with subacute combined degeneration of the spinal cord whereas this complication is frequently reported with the macrocytic or megaloblastic anemia that follows total gastrectomy.

Necessity of Bone-Marrow Biopsy

In the assessment of the hematologic picture after total gastrectomy a bone-marrow examination is essential since macrocytosis with a maximum mean corpuscular diameter of 8.5 microns from splenectomy alone can occur and can be very misleading if the peripheral-blood film alone is used.[45] Six of the patients described above had splenectomy with total gastrectomy. The diagnosis in all but 1 case was made from the presence of megaloblasts in the bone marrow.

The interval between removal of the stomach and onset of anemia or megaloblastic changes in the bone marrow exceeds the time limit described by Schwartz and Legree[46] for relapse of pernicious anemia after treatment has been discontinued. It is also well known that the patient with pernicious anemia cannot store large amounts of vitamin B_{12}. The normal human being appears to have a larger liver store of the vitamin B_{12} than these patients accumulate in remission. That one aspect of pernicious anemia is a defect of vitamin B_{12} storage is also a possibility.

Intestinal Sepsis

Some might argue that removal of the stomach has allowed gastrointestinal organisms with an avidity for vitamin B_{12} to ascend the gastrointestinal tract and hence to lead to deficiency in the host. The clinical response of patients with pernicious anemia to oral administration of chlortetracycline[47] supports this concept. Chlortetracycline and neomycin, however, do not change the absorption of orally administered cobalt^{60}-labeled vitamin B_{12}.[3]

Of the original explanations offered for the infrequent occurrence of pernicious anemia after total gastrectomy, the short duration of life in many cases and the administration of prophylactic therapy are the only conceivable ones on the basis of the data presented.

The observation and investigation of these 17 pa-

tients who have lived for many years after total gastrectomy with the development of megaloblastosis as the only major reflection of a gastric deficit suggest that intrinsic-factor production is the only absolutely essential function of the stomach in man. It is of interest that the sensation of appetite was little altered by operation, as previously noted in 1931 by Wangensteen and Carlson.[48] Although a normal appetite was present, satiety was achieved with less food. However, these patients ate at more frequent intervals, as governed by a sensation of hunger in most cases. This observation is at variance with a current view concerning the control of appetite, which states that the motor activity of the stomach produces hunger sensation, the basic factor regulating the ingestion of food.[49] The presence of food in the upper intestine after total gastrectomy undoubtedly inhibits the desire for food but cannot be explained as due to the liberation of enterogastrone.

Summary and Conclusions

Megaloblastic anemia indistinguishable from pernicious anemia is a late but inevitable sequela of total gastrectomy in patients who have not received prophylactic parenteral vitamin B_{12} or liver-extract treatment. With 1 exception, in all patients (11 in number) who underwent proved total gastrectomy at the University of Minnesota without prophylactic therapy for pernicious anemia and who survived for over three years a megaloblastic bone marrow developed. The one patient who did not have megaloblastosis lived longer than three years after total gastrectomy, but underwent hematologic examination two years and five months after operation. (Only 2 patients had these findings within less than three years of the operation and these were at two years, seven months, and eight months.) The total gastrectomy was performed for a wide variety of pathologic entities, which in addition to adenocarcinoma of the stomach included benign gastric ulcer, gastric polyps, hypertrophic gastritis, cardiospasm and esophagitis. Two of 13 patients who have lived for more than three years after total gastrectomy performed at the University of Minnesota Hospitals had received prophylactic therapy; neither patient has anemia although they are living eleven years and eight years after operation. In 4 patients who had undergone total gastrectomy at the Minneapolis Veterans Administration Hospital megaloblastic anemia was discovered more than three years after the operation.

The megaloblastosis is not related to the blind-loop anemia seen in animals and human subjects since it follows esophagoduodenostomy as well as esophagojejunostomy (loop or Roux-Y anastomosis). It is unlikely that these patients would all have had pernicious anemia without total gastrectomy, especially since 5 had free hydrochloric acid on gastric aspirations before operation.

The megaloblastic anemia that follows total gastrectomy responds completely to parenteral vitamin B_{12} therapy. Prophylactic folic acid therapy alone is not indicated, and vitamins containing it are considered hazardous because of the possible aggravation of the neurologic component of the deficiency.

Megaloblastosis after total gastrectomy is not believed to be due to sprue or a nutritional deficiency other than vitamin B_{12}, for the reasons outlined.

Intrinsic-factor production is the only essential function of the stomach in man.

All patients with total gastrectomy or proximal subtotal gastrectomy with esophagoantrostomy should receive prophylactic parenteral vitamin B_{12} or liver-extract therapy at least before three years after the operation and continuously thereafter.

The site of intrinsic-factor production in the human being corresponds to the area of the stomach pathologically involved in pernicious anemia (the body and fundus).

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ORGANIZED THROMBUS OCCLUDING A MAIN PULMONARY ARTERY

Report of Two Cases

S. T. LAUFER, M.D.,* AND J. D. GRAY, M.D.†

HALIFAX, NOVA SCOTIA, CANADA

THE number of published cases of obstruction by thrombus in the right or left pulmonary artery is few. Means and Mallory,[1] up to 1931, found 5 and added another. The case of Levy, Mayer and Jobard[2] and the 2 reported below bring the total to 9.

In addition to the apparent rarity of this condition, Levy et al.[2] succinctly emphasize its interest: "The cases of pulmonary thrombosis all come as surprises at autopsy — that is to say, the extreme difficulty of diagnosis is due not only to the great rarity of the condition but also to the clinical circumstances of its appearance."

CASE REPORTS

CASE 1. A 46-year-old woman, before the onset of her cardiac disability, had had frequent attacks of tonsillitis until the age of 12, when tonsillectomy was performed; hysterectomy was carried out at the age of 42.

At the age of 44, she had an attack of shortness of breath after a train accident. At that time, physical examination revealed a weight of 50.3 kg. (111 pounds), a height of 165 cm. (65 inches), a vital capacity of 2000 ml. and a hemoglobin of 76 per cent (Sahli). There were basal rales in the lungs. The right ventricle was enlarged on physical and x-ray examinations. Auscultation showed a presystolic murmur over the mitral and apical regions, with a snapping 1st and accentuated 2d sound over the pulmonic area. An electrocardiogram disclosed marked right-axis deviation, with a broad split P wave in Lead 2 and biphasic P waves in Leads V_1 and V_2 (Fig. 1 and 2). A diagnosis of mitral stenosis was made at that time. The patient was digitalized, with much improvement. Ten months later, a murmur occupying the entire diastole was noted. No systolic murmur was heard. The 2d sound was split.

Twenty-eight months later the patient had a slight hemoptysis accompanied by severe dyspnea and general weakness. Four days later transitory chest pain in the left anterior aspect of the chest was experienced. On the following day she had severe pain in the right lumbar region, aggravated by coughing and deep breathing, that required sedatives for relief. Auscultation of the heart revealed the presence of an apical systolic murmur with a musical character. The diastolic murmur had disappeared. It seemed that the mitral stenosis had become buttonhole in type, a contradiction in terms of the earlier findings. At this point the patient was admitted to the hospital, where examination showed marked cyanosis of the face, orthopnea, edema of the lower limbs, a large liver and a right-sided pleural effusion. The hemoglobin was 17.1 gm. per 100 ml., and the white-cell count 15,400, with 80 per cent neutrophils, 17 per cent lymphocytes and 3 per cent monocytes. The blood urea nitrogen was 86 mg. per 100 ml. The potassium was 6.3 milliequiv., the sodium 129 milliequiv., and the chloride 110 milliequiv. per liter, and the carbon dioxide combining power was 38.5

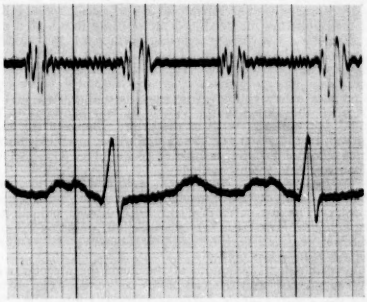

FIGURE 1. *Apical Tracing Taken on November 5, 1952, in Case 1.*

Note the split and broad P waves. The murmur in diastole occupies at times the whole of diastole; at times it is presystolic.

*Cardiologist, Halifax Infirmary.
†Pathologist, Halifax Infirmary.

vol. per cent. The urine contained albumin but no red blood cells. With appropriate therapy, the blood urea nitrogen fell to normal.

In the hospital the character of the heart sounds again changed, with the development of a blowing systolic murmur, loudest at the apex and at the left border of the sternum near the 4th interspace. A 3d sharp sound was also heard at the apex. X-ray study showed a prominent pulmonary conus, with enlargement of the right ventricle and atrium. The patient's condition gradually deteriorated and she died 2 months after admission.

At autopsy the right pleural cavity contained about 4 liters of straw-colored fluid; the left was dry. The lower

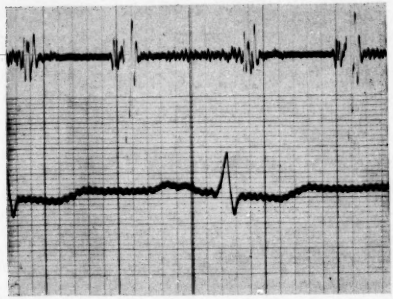

FIGURE 2. *Apical Tracing Taken on August 4, 1953, in Case 1.*

lobe of the right lung showed a gross pulmonary infarct. The transverse diameter of the heart was markedly increased, owing principally to dilatation and hypertrophy of the right ventricle. The left ventricle was normal. Both atria showed gross muscle hypertrophy. The tricuspid valve was incompetent. The mitral valve had been replaced by a calcified mass that had reduced the opening to a hole 5 mm. in diameter. On the ventricular surface of the calcified mass were a large number of small, loosely adherent, partially calcified concretions. The aortic valves were not remarkable. The pulmonary ring was distended. The right pulmonary artery contained an organized thrombus that all but filled the lumen of the vessel. It was adherent to the lateral and posterior walls of the artery. Between the superior wall of the vessel and the thrombus was a slitlike lumen, which allowed for the passage of blood (Fig. 3). The left pulmonary artery was normal.

The foramen ovale was patent and had been markedly dilated. Both atrial appendixes contained small mural thrombi. The cut surface of the liver showed typical nutmeg changes. The right kidney was small, weighing 90 gm.; the lower pole had been replaced by a massive white infarct. The left kidney was normal.

On histologic examination of the lung, the alveolar walls were edematous, and the capillaries congested. The alveoli were filled with exudate containing heart-failure cells. The small and medium pulmonary vessels showed marked intimal proliferation, with a concomitant reduction of the lumen. In some areas an organized thrombus was present. The larger vessels appeared normal. The pulmonary veins were grossly distended. The liver demonstrated marked passive venous congestion. The spleen was engorged with red blood cells.

The infarcted area of the kidney showed coagulation necrosis, with fibrous-tissue replacement. The interstitial renal vessels in the involved area were filled with thrombus. The remainder of the kidney tissue was normal.

The myocardium showed interstitial edema, perivascular fibrosis and brown atrophy. Aschoff's bodies could not be demonstrated on serial sections.

CASE 2. A 2½-year-old girl was a 15th child delivered prematurely by cesarean section because of placenta praevia. Her birth weight was 1.8 kg. (4 pounds), and her weight on admission to the hospital 5.9 kg. (13 pounds). She had been artificially fed, and her vitamin D intake had been erratic. She first sat up at 19 months, but did not stand; she had her 1st tooth at 1 year, and could say single words. Physical examination showed the typical facies of mongolism, pallor, hypotonia, a congenitally narrowed auditory meatus and markedly dilated veins over the forehead. The mouth contained a few misshapen teeth. Harsh breath sounds were heard at the base of the right lung. The heart and abdomen were normal. There was no clubbing of the fingers and no cyanosis.

The red-cell count was 2,140,000, with a hemoglobin of 24 per cent (Sahli), and the white-cell count 8300, with a normal differential. The alkaline phosphatase was 9 King–Armstrong units. The Wassermann reaction was negative, and the Kahn reaction positive. X-ray study of the skeleton showed a generalized increase in bone density.

Six days after admission the patient had a brisk hematemesis that required transfusion for treatment; 3 days later bronchopneumonia developed. An x-ray film of the chest taken at this time demonstrated a pulmonary conus.

Thirteen days later another x-ray film of the chest showed resolving pneumonia and a globular heart. The pulmonary conus was no longer present. Nine days later, while apparently convalescing from the pneumonia, she suddenly died.

At autopsy the left lung was shrunken in size in comparison with the right, giving an atelectatic appearance. The

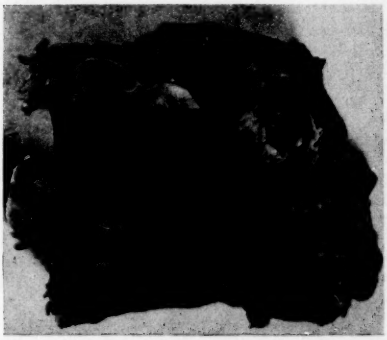

FIGURE 3. *Right Pulmonary Artery in Case 1, Showing the Thrombus in Situ.*

right middle lobe was partly consolidated. The heart was grossly abnormal. The right ventricle and atrium showed marked hypertrophy of the muscle, whereas the musculature of the left ventricle and atrium was normal. The pulmonary conus was dilated, and the tricuspid valve incompetent. When the pulmonary artery was opened a large calcified thrombus was seen, originating about 6 mm. above the valves and entering the left pulmonary artery; it filled the lumen completely. The thrombus could be followed in the ramifications of the artery as it spread to the lung periphery (Fig. 4). The mitral and aortic valves were normal. The aorta was not remarkable, but the left bronchial artery was enormously dilated from its aortic origin onward. Except for a hemorrhagic duodenitis and a rectum full of blood, the rest of the post-mortem examination was not remarkable.

Subsequent qualitative analysis of a portion of the thrombus showed the presence of calcium, carbonates, phosphates, urates and fibrin.

On histologic study areas taken from the right lung demonstrated patchy collapse and emphysema. Most of the alveoli were filled with an exudate in which heart-failure cells lay. The alveolar walls were edematous and showed marked capillary congestion. Some of the bronchi were filled with exudate, and others were clear. In the pneu-

monic area were patches of necrotic tissue. The vessels examined were free of both intimal and medial hypertrophy. Sections taken from the left lung disclosed complete distortion of the normal alveolar architecture. The walls were compressed, distorted and replaced by fibrous tissue showing a few dilated blood vessels, some filled with blood. The pulmonary-artery vascular bed contained calcified thrombi (Fig. 5).

The bronchi were relatively normal. The heart muscle showed interstitial edema with small scattered foci of coagulation necrosis involving the muscle fibers and apparently related to an obliteration of many of the capillaries by endothelial proliferation but without concomitant small-round-cell cuffing. The arterioles were normal.

Discussion

During life, Case 1 presented a series of diagnostic difficulties. The onset of acute pulmonary edema occurred in a patient unaware of ever having had rheumatic heart disease, undiscovered in spite of previous competent medical attention. An extraordinarily rapid, continuous increase in the size of the heart followed the onset of the pulmonary edema, with relatively

Figure 4. *Calcified Thrombus in the Left Pulmonary Artery in Case 2, and Its Distribution in the Lung Tissue.*

little dyspnea and orthopnea. After the hemoptysis, the diastolic murmur disappeared, and an apical musical systolic murmur developed. Cyanosis increased markedly, out of proportion to the inferred valvular involvement. The sudden onset of apparent acute renal failure further complicated the patient's condition.

The post-mortem findings accounted for the variegated clinical pictures. The dilated patent foramen ovale afforded the patient protection against the effects of the mitral stenosis for a number of years. The patency of the foramen ovale explains the presence of the diastolic murmur, which was evidently due to the intra-atrial regurgitation of blood that masked the usual auscultatory features of a buttonhole mitral-valve lesion. This murmur disappeared with the onset of pulmonary thrombosis and was replaced by the

Figure 5. *Section from the Left Lung in Case 2, Showing Fibrous-Tissue Replacement of the Normal Alveolar Walls, a Few Scattered Dilated Blood Vessels and Calcified Thrombi Lying in the Pulmonary-Artery Vessels (Hematoxylin and Eosin Stain X170).*

typical sounds of the buttonhole type of mitral stenosis.

It seems reasonable to assume that the chain of events leading to the alteration in heart sounds and increased cyanosis was related to the sudden increase in pulmonary circulatory pressure caused by the formation of the large thrombus in the right pulmonary artery. The atrial pressure differences disappeared and eliminated the regurgitant feature. The characteristic signs of uncomplicated marked mitral stenosis then became evident. The same mechanism also explains the sudden further enlargement of the right ventricle.

The changes observed in this patient over the last two years of life support the contention of Dexter et al.[3] that the apparent discrepancy of a gradual increase in heart size without concomitant dyspnea is due to a low fixed cardiac output as a result of a balance between the continuously growing pulmonary resistance on the one side and the reduced outflow through the buttonhole stenosis on the other. In this

patient, the exacerbation of the pulmonary hypertension due to the thrombus upset this balance and led to hemoptysis, pulmonary edema, hepatomegaly and dependent edema.

It is of interest that the sudden appearance of nitrogen retention was due not to peripheral circulatory collapse, or solely to congestive heart failure, but to gross renal infarction. The absence of red cells in the urine did not support the clinical suspicion of renal infarction. The cause of the nitrogen retention was left in doubt and only clarified by the post-mortem findings.

In Case 2 pulmonary-artery thrombosis was not suspected clinically. It is evident that a slowly growing block to the pulmonary circulation is not an immediate threat to life, for the calcification of the thrombus and the fibrous replacement of the affected alveolar tissue must have been present for at least half this young patient's life. The effect of the alteration in pulmonary blood flow that eventually led to heart failure was minimized by the presence of mongolism, with its concomitant hypotonia and a vegetative existence demanding little of the myocardium.

It may be noted that the increased collateral circulation through the bronchial artery was insufficient to meet the nutritional demands of the lung tissue on the affected side and led to fibrous-tissue replacement.

Summary

The diagnostic difficulties attending a case of buttonhole mitral stenosis with a patent foramen ovale, complicated by an organized thrombus in the left pulmonary artery, with survival for a considerable period, are reported. The question of the etiology of pulmonary hypertension in the production of such thrombi is raised.

In another case pulmonary-artery thrombosis was not suspected clinically but eventually led to heart failure, which was minimized by the presence of mongolism, with its concomitant hypotonia and vegetative existence of the patient.

These two cases raise the total number reported to date to 9.

The clinical consequences of pulmonary-artery thrombosis are briefly discussed.

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CLINICAL CORRELATES OF THE KIMMELSTIEL–WILSON LESION*

Franklin H. Epstein, M.D.,† and Vito Joseph Zupa, M.D.‡

New Haven, Connecticut

THE clinical and pathological features of intercapillary glomerulosclerosis have received considerable attention since this entity was described in 1936 by Kimmelstiel and Wilson.[1] Numerous reports attest to the occurrence of profuse albuminuria, hypoalbuminemia and edema, usually in association with hypertension and a distinctive retinopathy, in diabetic patients in whom glomerulosclerosis is demonstrated at autopsy.[1-10] Many features of the disease, however, remain unclear. There is disagreement about the relative frequency or importance of associated conditions such as pyelonephritis and congestive heart failure. It is held, on the one hand, that the disease has a predilection for elderly women with mild diabetes[2] and, on the other, that it is commonest in young males.[4] It has even been suggested that, in contrast to other patients with diabetes, patients with nodular glomerular lesions have a unique metabolic defect that manifests itself in a tendency for the insulin requirement to decrease as the disease progresses, and in a striking rarity of episodes of diabetic acidosis.[11] This has been disputed by Runyan et al.[12]

To clarify some of these questions, as well as to obtain more information about the natural history of the Kimmelstiel–Wilson syndrome, experience with this disease at the New Haven Hospital from 1944 to 1953 was reviewed.

Methods

One hundred and thirty-seven pathological protocols, comprising all patients with diabetes autopsied between 1944 and 1953, were perused, and the sections of kidney tissue stained with hematoxylin and eosin were reviewed; 37 patients (27 per cent) had nodular glomerular lesions of the type described by Kimmelstiel and Wilson,[1] Allen[13] and Bell.[14] Only kidneys with typical eosinophilic nodules in the glomerular tufts were selected, because of the undisputed association of these characteristics with the glomerulosclerosis of diabetes mellitus.[13,14] Sections

*From the Department of Internal Medicine, Yale University School of Medicine.

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†Assistant professor of internal medicine, Yale University School of Medicine; associate attending physician, Grace-New Haven Community Hospital.

‡Rotating intern, Lenox Hill Hospital, New York City.

of the kidneys were graded according to the number of glomeruli out of 20 that contained nodules, as follows: Grade 1, 1 to 5; Grade 2, 5 to 10; Grade 3, 10 to 15; and Grade 4, 15 to 20 glomeruli. The clinical records of these patients were then reviewed.

The nature of the study did not permit selection of a "control series" in the strict sense. With this limitation in mind, the clinical records of 37 autopsied cases of diabetes without histologic evidence of nodular glomerulosclerosis were selected at random and similarly investigated for comparison. Patients with diabetes of less than one year's duration, or whose clinical or pathological records contained inadequate data, were excluded from this latter group.

Results

Renal Pathology

About a third (12) of the 37 patients in the Kimmelstiel–Wilson group had nodular glomerular lesions of Grade 1 or 2; a third (13) were graded 3, and the remaining third were graded 4 (Table 1). Pyelonephritis was present in 76 per cent, in some as an obviously acute or terminal manifestation. Arteriosclerosis of the larger renal vessels, as well as arteriolosclerosis of varying severity and extent, was present in every case. Reflecting these pathological findings, an elevated nonprotein nitrogen (40 mg. per 100 ml.) was noted at some time during the clinical course of 22 patients (60 per cent) and 12 patients died with a nonprotein nitrogen of over 100 mg. per 100 ml.

In the comparison series, 23 patients (62 per cent) had arteriolosclerosis, but arteriosclerotic lesions of the larger vessels were prominent in only 7. Pathological evidence of pyelonephritis was present in 8 patients (22 per cent). Nodular glomerulosclerosis was entirely absent in all kidneys. As might have been expected, an elevated nonprotein nitrogen was recorded in only 3 patients of this group.

Age, Sex and Duration of Diabetes

Twenty-eight of the 37 patients in the Kimmelstiel–Wilson group were women (Table 2). The average age at death was fifty-five. These statistics did not differ strikingly from those characterizing the group of diabetic patients without glomerulosclerosis.

In patients with Kimmelstiel–Wilson lesions, diabetes appeared as early as nine years of age and as late as the eighth decade; the average age at onset was forty-one. The patients in this group lived from five to twenty-five years (average, fourteen and three-tenths years) after the diagnosis of diabetes was established. In the group of patients without glomerulosclerosis, the average age at which diabetes appeared was fifty-one, and the average duration was nine years before death.

Hypertension and Albuminuria

A blood pressure above 150 systolic, 90 diastolic, was consistently recorded in 30 (80 per cent) of 37 patients with Kimmelstiel–Wilson lesions (Table 2).

Table 1. *Renal Pathology.*

Group	No. of Patients	Patients with Pyelonephritis	Patients with Arteriolosclerosis	Patients with Arteriosclerosis	Patients with Nodular Glomerulosclerosis			
					Grade 1	Grade 2	Grade 3	Grade 4
Patients with Kimmelstiel–Wilson lesions	37	28	30	37	5	7	12	13
Patients without Kimmelstiel–Wilson lesions	37	8	23	7	—	—	—	—

Table 2. *Clinical Features.*

Group	Male Patients	Female Patients	Average Age at Death	Duration of Diabetes	Patients with Hypertension*	Average Duration of Hypertension	Patients with Persistent Albuminuria	Average Duration of Albuminuria	Patients with Neuropathy	Patients with Retinopathy	Patients with Edema	Patients with Hypoalbuminemia†	Patients with Congestive Heart Failure	Patients with Elevated Nonprotein Nitrogen‡
			yr.	yr.		yr.		yr.						
Patient with Kimmelstiel–Wilson lesions	10	27	55	14	30	6	32	3.5	20	30	30	22	25	22
Patients without Kimmelstiel–Wilson lesions	15	22	60	9	23	6	2	5.0	13	9	12	7	12	3

*Blood pressure of 150/90.
†Serum albumin of less than 3 gm. per 100 ml.
‡Level of 40 mg. per 100 ml.

The average duration of hypertension before death was five and eight-tenths years, with a range of one to twenty-one years. Seven patients were not noted to have hypertension although post-mortem examination revealed nodular glomerular lesions ranging in severity from Grade 1 to Grade 4. Albuminuria was present in 32 patients (86 per cent). The gloomy import of this sign is emphasized by an average length of life of only three and a half years (range one to seventeen years) after its detection. Six patients lived for more than five years, and 2 as long as ten years, after the appearance of both albuminuria and hypertension. Coexisting pyelonephritis and congestive heart failure undoubtedly contributed to proteinuria in many cases. In 5 patients, 4 of whom had hypertension, albuminuria was never noted. Only 1 patient had neither albuminuria nor hypertension although +++ nodular glomerulosclerosis was present at autopsy.

TABLE 3. *Average Insulin Requirement and Frequency of Acidosis.*

Average Insulin Requirement	Patients with Kimmelstiel–Wilson Lesions		Patients without Kimmelstiel–Wilson Lesions	
	No. of patients	No. with acidosis	No. of patients	No. with acidosis
units				
0-10	17	4	22	5
10-30	11	3	6	3
30-60	9	7	9	6
Totals	37	14	37	14

In the comparison group, 62 per cent had hypertension, which had existed an average of six years before death. This frequency illustrates the high degree of association between diabetes and generalized vascular disease, and emphasizes the fact that the appearance of an elevated blood pressure in a diabetic patient does not necessarily imply the presence of nodular glomerulosclerosis. Persistent albuminuria was noted in only 1 patient of this group, in whom chronic pyelonephritis and hypertension had been present for fourteen years. Diabetic glomerulosclerosis might well have been wrongly suspected from such clinical findings.

Retinopathy and Neuropathy

Eighty per cent of the patients with Kimmelstiel–Wilson lesions (Table 2) also had "diabetic" retinopathy,[15] consisting of capillary aneurysms and pinpoint hemorrhages. By contrast, in the records of only 30 per cent of the patients without nodular glomerulosclerosis, were these findings remarked upon. Absent tendon reflexes, diminished vibratory and position sense, paresthesias, shooting pains and autonomic-nervous-system dysfunction, singly or in combination, were present at some time in 54 per cent of the group with Kimmelstiel–Wilson lesions but in only 35 per cent of the comparison series. The longer average duration of diabetes in the former patients, as well as the greater care and frequency with which they were examined, may have been partly responsible for these discrepancies.

Edema, Hypoalbuminemia and Heart Failure

Dependent edema was present in 80 per cent of the patients with glomerulosclerosis and, as expected, was associated with hypoalbuminemia (level of less than 3 gm. per 100 ml.) in three quarters of these (Table 2). A striking finding, however, was the presence of additional signs and symptoms of congestive heart failure in 83 per cent at the time that edema was prominent. These consisted of basilar pulmonary rales, a prolonged circulation time or an enlarged liver that became smaller with bed rest and digitalis. In many cases edema subsided or diminished at least temporarily after digitalization. It appears that a failing heart frequently contributes to edema developing in the course of diabetic glomerulosclerosis.

Insulin Requirements

Patients with intercapillary glomerulosclerosis required little or no insulin, moderate amounts or relatively large amounts, in approximately the same proportions as patients without Kimmelstiel–Wilson lesions (Table 3). Six patients with intercapillary glomerulosclerosis noted a decrease of at least 15 units in their requirements of insulin during the terminal stages of their disease. Five of these died with severe renal impairment, after a course marked by anorexia and associated with varying degrees of starvation.[12]

Frequency of Diabetic Acidosis

At least 1 episode of diabetic acidosis was documented in 14 (38 per cent) of the 37 patients with Kimmelstiel–Wilson disease (Table 3). In 12 of these, the pathological classification was +++ or ++++. Diabetic acidosis was not diagnosed from the record unless all the following criteria were present: high blood sugar; low carbon dioxide content of the serum; ketonuria; and increase in requirement of insulin. Nine patients had repeated episodes of acidosis, and in 4, acidosis was a terminal event. One patient (M.B., N.H.H. 8955), who was twenty-six years old at the time of death, had been admitted to the hospital for diabetic acidosis over sixty times since the age of nine. The typical glomerular nodules found at post-mortem examination in this patient are shown in Figure 1. Diabetic acidosis also occurred in 14 of 37 patients without Kimmelstiel–Wilson lesions. *The frequency of diabetic acidosis in patients with nodular glomerulosclerosis, therefore, did not differ from that observed in diabetic patients without this lesion.*

Discussion

Although it has repeatedly been emphasized[2] that the Kimmelstiel–Wilson lesion is most common in

diabetic patients forty to sixty years of age, with women outnumbering men by two to one, it must not be forgotten that the over-all incidence of diabetes rises sharply at this time of life and that twice as many women as men are destined to have the disease.[16] In the present series, as in the larger one of Rogers et al.,[6] the age and sex distribution of patients with Kimmelstiel–Wilson lesions was similar to that of diabetic patients without glomerulosclerosis.

The large number of cases of persistent albuminuria, hypertension, retinopathy and neuropathy, as well as cardiac and renal failure, among the patients with nodular intercapillary glomerulosclerosis is in agreement with previous reports.[1-10] Although it is possible for nodular glomerulosclerosis to occur in the absence of either persistent albuminuria or hypertension, in only 1 patient of the present series were both these findings absent. On the other hand, an elevated blood pressure is extremely common in diabetes without nodular glomerulosclerosis. A mistaken clinical diagnosis of Kimmelstiel–Wilson disease may therefore be made in a diabetic patient in whom hypertension, albuminuria, edema and retinopathy are associated with pyelonephritis or nephrosclerosis alone.[17]

The importance of heart failure as a factor, in conjunction with hypoalbuminemia, in the formation of edema in these patients is emphasized by the present data. With a lowered serum oncotic pressure secondary to hypoalbuminemia, the increase in central venous and peripheral capillary pressures necessary to produce increased transudation is correspondingly smaller, and an elevated venous pressure may therefore not be detected clinically. The physician's responsibility for undertaking a careful therapeutic trial of digitalis in these circumstances is apparent.

The renal lesion of intercapillary glomerulosclerosis is not known to be reversible. However, the striking frequency of acute and chronic pyelonephritis, which complicated the present series and undoubtedly contributed to renal impairment, suggests that prompt and vigorous treatment of urinary infections, as well as their prevention (for example, by avoiding unnecessary catheterizations), may prolong life and postpone the appearance of renal decompensation in some patients.

Zubrod, Eversole and Dana[11] reported that of 41 patients with intercapillary glomerulosclerosis, 56 per cent needed considerably less insulin during their last months or years of life. Only 2 of their patients ever had an episode of diabetic acidosis. These authors postulated that the Kimmelstiel–Wilson lesion was associated with a specific type of diabetes, characterized by progressive amelioration in severity, and infrequent episodes of diabetic acidosis. In the present series, however, only 6 patients (16 per cent) had a substantial decrease in insulin requirement before death. This may have been due to a lower intake of food, as suggested by Runyan et al.,[12] or to a diminished concentration of glucose in the urine associated with hyposthenuria and decreased glomerular filtration, without a decline in blood sugar.[18,19] Diabetic acidosis occurred with equal frequency in patients with and without glomerulosclerosis, and was documented after, as well as before, the clinical syndrome of hypertension, albuminuria and edema had fully developed. The present data, therefore, do not support the thesis of Zubrod, Eversole and Dana that a specific type of metabolic defect is associated with the nodular glomerular lesion that Kimmelstiel and Wilson described.

FIGURE 1. *Typical Nodular Glomerulosclerosis in a Diabetic Patient Who Was Admitted to the Hospital in Diabetic Acidosis over Sixty Times in Seventeen Years.*

SUMMARY

The clinical courses of 37 diabetic patients with nodular intercapillary glomerulosclerosis and of 37 without this lesion are reviewed.

The age and sex distribution was similar in the two groups.

Persistent albuminuria, hypoalbuminemia, hypertension, neuropathy, retinopathy, cardiac failure and renal decompensation were frequent among patients with intercapillary glomerulosclerosis.

Nodular intercapillary glomerulosclerosis was always associated with sclerosis of large and small renal vessels, and frequently with pyelonephritis.

Intercapillary glomerulosclerosis was found in patients with all levels of basal insulin requirement. In only 6 patients with this lesion was a decreased requirement of insulin noted terminally.

Diabetic acidosis occurred at least once in 14 of 37 patients with nodular glomerulosclerosis.

The present study does not support the view that a specific or unique type of diabetes, characterized by infrequent episodes of acidosis and a decreasing requirement of insulin, is associated with the nodular glomerular lesion of Kimmelstiel and Wilson.

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MEDICAL PROGRESS

CARCINOMA OF THE BREAST (Continued)*

The Study and Treatment of the Patient

ANDREW G. JESSIMAN, F.R.C.S.,† AND FRANCIS D. MOORE, M.D.‡

BOSTON

IV–The Role of Breast Surgery

Biopsy

The folly of undertaking or withholding treatment of the small breast lump without histologic study has been emphasized and re-emphasized for years. It remains folly; but this should not blind us to two facts:

Excision is safer than incision. If one cannot circumincise the lesion freely in normal tissue, a simple mastectomy may in itself provide the best biopsy. One should not knowingly cut across disease in this initial approach.

When cancer is obvious by all physical signs, and characteristic metastases are present, one should not endanger the patient by a compulsive desire for immediate histologic proof. Preliminary x-ray treatment, biopsy of small, freely movable nodes or even needle biopsy is better than frontal assault on a massive local lesion for confirmation of an obvious diagnosis.

Local Surgery for the Early Lesion

Considerable controversy has arisen over the application of radical mastectomy in the early case. Urban,[68] Urban and Baker[69] and Wangensteen[70] were influenced by Handley's[46] work showing the frequent spread of cancer cells to the internal mammary chain, particularly from lesions in the medial half of the breast. Believing that the prime object of radical cancer surgery is the *en bloc* excision of the primary cancer together with its regional lymph nodes, they have attempted to accomplish this by extending the standard operation to include excision of the lateral half of the sternum, costal cartilages and underlying internal mammary vessels and lymphatic chains and in some cases combining this with a supraclavicular-node dissection.

We do not believe that any improvement in the final results will be achieved by this and agree with Fisher,[71] who states:

> If the surgeon were sure that the limit of metastatic involvement was the chain of nodes along the internal mammary vessels, then there would be some justification for removing the costal cartilages and excising the tissues in the anterior mediastinum. However, experience has shown that this situation is never present and that the pathological sequence in the life history of carcinoma of the breast cannot be measured in terms of a few lymph node excisions.

If one may generalize from carcinoma in other locations, it is most exceptional for extension of lymphatic dissection to improve prognosis when nodes are already massively involved. If they are not involved, the rationale for further extension is questionable. An expeditious radical mastectomy of the standard type will clear the axilla satisfactorily.

McWhirter[72] advocates simple mastectomy combined with x-ray therapy (3750 r) to the supraclavicular, internal mammary and axillary regions on the grounds that the standard radical mastectomy cuts across the lymphatic field and will disseminate

*From the Department of Surgery, Peter Bent Brigham Hospital, and Harvard Medical School.

†Henry E. Warren Fellow and assistant in surgery, Harvard Medical School; junior associate and cancer co-ordinator, Peter Bent Brigham Hospital.

‡Moseley Professor of Surgery, Harvard Medical School; surgeon-in-chief, Peter Bent Brigham Hospital.

the cancer and that it is only effective in 36 per cent of patients referred for surgery. In the remainder the disease will have spread either to the internal mammary or the contralateral axillary lymph nodes. McWhirter argues that a super-radical mastectomy will only be beneficial at a maximum in 56 per cent of cases, whereas local mastectomy and irradiation may be of assistance in 85 per cent. By his view the site of the tumor is no longer of importance, for he believes that lesions in the medial half of the breast with spread to the internal mammary lymphatics can be as effectively treated as those with axillary lymphatic spread.

Ackerman,[73] in an analysis of McWhirter's cases, points out that his results must be critically studied because 220 out of 719 patients received immediate x-ray "sterilization" and excision of nodes. Stilbestrol and testosterone therapy were added to the treatment whenever there was manifest evidence of persistence of the disease. No histologic proof was offered of destruction of the cancer cells in the lymph nodes, and, in fact, many of the nodes excised showed the presence of active disease. No objective evidence was supplied to prove that the surgical operation of simple mastectomy did not disseminate the disease as much as the radical operation, and, finally, severe irradiation changes developed in 47 cases.

Despite such adverse criticism, McWhirter has rightly re-emphasized the principle that meddlesome surgery in the midst of advancing invasive cancer, as in the involved axilla, is a hazard to the patient. The disease is disseminated by the knife. As will be seen below, this principle is directly applicable in the Stage 2 lesion. In these cases, with frank axillary involvement, the McWhirter regimen or some similar approach offers a better survival rate and possibly a lower mortality than radical surgery. As of this time we know of no proof that the Stage 1 lesions should be treated other than by removal with the first nodal barrier in the axilla. This offers the only chance for true cure by total eradication, achieved in about 65 per cent of the Stage 1 cases by radical mastectomy. The extreme importance of careful physical examination is pointed up by this fact: the presence of large or multiple axillary metastases now constitutes a positive contraindication to radical mastectomy.

V–Endocrine Treatment: Medication and operation

Endocrine Medication

Nathanson and Kelley[1] stated in their 1952 review, ". . . theoretically it can be postulated that under various circumstances, estrogens, androgens and castration temporarily restore a substrate that is hostile to the growth of breast cancer."

The invariable reactivation of the lesion after a favorable response suggests an adaptation of the more resistant cells to an environment originally rendered unfavorable to tumor growth. Some lesions may again regress when all hormone therapy is withdrawn or when a new hormone is substituted. This suggests that the lesions are still susceptible to alterations in their physiologic and metabolic environment.

Estrogens.

The most favorable cases. The therapeutic use of estrogens should be reserved for patients in the "senile" age group: soft-tissue lesions respond more readily than osseous deposits. The danger of stimulating the disease constitutes a definite contraindication to estrogen administration within twenty years of the menopause. A stilbestrol test should always precede prolonged use.

Preparations and dosage. Several preparations are available: stilbestrol, dienestrol and Estinyl. Effective therapy can be carried out by the use of stilbestrol, 15 mg. per day by mouth, the course lasting three months or more if progress is maintained. If an exacerbation occurs during therapy, a further remission may be obtained by stopping of the hormone. Massive doses, 200 mg. per day, have been used with good effect to inhibit pituitary function.

Side effects and dangers. Salt and water retention may lead to worsening of heart failure. Painful breasts, uterine bleeding and nausea and vomiting may occur. The danger of hypercalcemia has been mentioned previously.

Results to be expected. Subjective and objective results correlate closely. Most authors[1,6,61,74] agree that in the older age group, 40 per cent of soft-tissue and 30 per cent of osseous metastases will improve for a time.

Androgens.

The most favorable cases. Androgens are possibly most useful in the younger, premenopausal or menopausal age group. They are particularly effective in osseous metastases or in the treatment of patients suffering a relapse after adrenalectomy.[35]

Preparations and dosage. Testosterone propionate, methyl testosterone and cyclopentyl propionate are used. The most widely used and effective substance is testosterone propionate, given intramuscularly in a dosage of 150 mg. thrice weekly. A subcutaneous implant of testosterone propionate can be used effectively as a second course of testosterone therapy.

Side effects and dangers. Masculinizing effects are produced, such as hirsutism, deep voice, acne, enlargement of clitoris, changes in temperament and libido and gain in weight. The patient must be forewarned of these changes, which are often severely limiting. If the disease is stimulated, the signs of hypercalcemia will occur. Stimulation of the disease by testosterone raises the possibility of its conversion to estrogen.[75]

Results to be expected. Symptomatic improvement is much more common than objective improvement. The latter, manifested by healing of osseous lesions and decrease in size of the primary tumor or of parenchymal disease, is seen in only 20 per cent of cases.[35,61]

Cortisone and analogues.

Mechanisms of action. An initial high "loading dose" of cortisone inhibits pituitary production of ACTH and produces adrenocortical inhibition. This can be maintained on a reduced dosage.*

Evidence suggests that cortisone also acts by competing with estrogen in the peripheral blood for active sites on the protein molecule, which is the carrier for estrogens in the blood stream. Szego and Roberts[76] postulate that corticoids bind more weakly with this protein molecule than estrogens, which can only be replaced when cortisone is present in large excesses. This would explain the phenomenon of the ultimate "escape" of the disease from the control achieved by cortisone, for in these patients estrogen production, increasing with time, eventually exceeds the limit that can be "bound" by the standard dose of cortisone (50 mg.).

Pearson et al.[35] have shown that a further remission may be achieved by large doses of cortisone in patients who have relapsed after previous gonadectomy, adrenalectomy and hypophysectomy. Cortisone must be acting directly on the disease itself in such cases.

Preparations and dosage. Cortisone by mouth, prednisone (Meticorten), cortisone acetate intramuscularly, hydrocortisone intravenously and fluorohydrocortisone are used. The dosages of all but fluorohydrocortisone and prednisone are the same; the route of administration is determined by the patient's ability to take oral medication and by the need for speed in the establishment of a high blood level. Adrenal suppression is achieved by 150 mg. per day by mouth for three days and reduced by 25 mg. per day every third day until the maintenance dose of 50 mg. per day is reached. A dose of 300 to 400 mg. of cortisone per day in the terminal stages may control the disease temporarily.

Fluorohydrocortisone has great salt-retaining properties, is more powerful than cortisone and can produce adrenal suppression on a dosage rate of 5 mg. per day. Prednisone is used in a dose of 24 to 30 mg. per day.

*There has been a tendency to equate cortisone administration ("cortisone inhibition") with surgical adrenalectomy, an implication involved in such terms as "medical adrenalectomy." It must be emphasized that steroid medication results in an endocrine imbalance quite different from that produced by ablation of either ovaries or adrenal glands. Under cortisone administration, both adrenal and pituitary function is inhibited; after adrenalectomy there is an immediate upsurge of pituitary function so far as secretion of ACTH and possibly other hormones is concerned. It is not difficult to imagine a patient with a pituitary-stimulated tumor much improved on cortisone and yet undergoing marked deterioration after adrenalectomy.

Side effects. Salt and water retention may cause edema and cardiac failure or pulmonary edema. The changes of Cushing's disease, the development of a "moon face" and aggravation of diabetes are seen. Peptic ulceration may occur, possibly prevented by the administration of Gelusil and an ulcer diet. Prolonged cortisone dosage produces osteoporosis. This is an indication for the simultaneous administration of testosterone.

Results to be expected. Remissions produced by adrenal inhibition with cortisone often last only four to six months, although longer periods of remission, of eighteen months or more, have been reported.[77,78]

The following case illustrates the sort of result occasionally observed in long-term cortisone treatment.

M.M. (P.B.B.H. U 36),† a 53-year-old woman, in 1946 underwent a radical mastectomy for carcinoma of the right breast. In 1950 a 2d carcinoma was noted in the left breast, and osseous metastases were demonstrated at this time. A simple mastectomy on the left was performed.

In 1951 she sustained a pathologic fracture of the right humerus. In February, 1953, a bilateral oöphorectomy was performed, and she received a remission of 6 months, but by August, 1953, her disease was advancing, and between this time and April, 1954, she suffered many pathologic fractures.

She was admitted to the Peter Bent Brigham Hospital in April, 1954, in a terminal condition, bed ridden and cachectic, and with physical findings of hepatomegaly, ascites and numerous pathologic fractures. Laboratory investigations revealed a serum calcium of 7.2 milliequiv. per liter, a 24-hour urine calcium excretion of 1000 mg. and urine estrogen values of To 120 I.U. and Tzn 1150 I.U.

When placed on cortisone, 50 mg. per day, she made a dramatic recovery, and by June, 1954 (8 weeks later), she was free of pain, and the ascites had gone. Laboratory investigations revealed a calcium of 5.2 milliequiv. per liter, a urine calcium excretion of 40-50 mg. per 24 hours, with urine estrogens, To 45 I.U. and Tzn 350 I.U. Improvement was maintained for 16 months before relapse.

Endocrine Surgery

Castration.

Indications. Prophylactic castration has been shown to be of benefit in protection both against development of the disease and against further spread. It is our belief that all women suffering from this disease while in the menopausal or premenopausal age group should be castrated. The value of this procedure is well proved. Its use should be extended to the menopausal age group when the ovaries are found to be producing large quantities of estrogens by assay[14,15] and may show cortical stromal hyperplasia.

Technical notes. This simple operative procedure throws little strain on the sick patient.

Endocrine care. None is needed. Hot flashes, which may be troublesome, should *not* be treated with estrogens.

Results to be expected. About 40 to 50 per cent of patients in the younger age group and a smaller percentage in the older group show good results.

†This case is to be reported in detail elsewhere by Jessiman and Emerson.[79]

Osseous lesions recalcify, soft-tissue disease regresses, pleural effusions and ascites become absorbed, and these objective signs are accompanied by relief of bone pain, feelings of well-being and increased appetite.

The results of castration in the male are even more gratifying, about 70 per cent of these patients showing good subjective and objective responses.

The following case illustrates a positive stilbestrol test and a favorable castration response in a postmenopausal woman with cortical stromal hyperplasia:

E.B. (P.B.B.H. 5J887), a 72-year-old woman, underwent radical mastectomy for carcinoma of the left breast in 1952. In June, 1955, pain in the back developed and osseous metastases were demonstrated. In November she was admitted to the Peter Bent Brigham Hospital.

She had nursed 3 children, each for 2 years; natural menopause had occurred at 50 years of age.

On examination her endocrine age was considered to be less than her true age. There was no evidence of recurrent or metastatic disease.

X-ray study revealed numerous osseous metastases.

A stilbestrol stimulation test was carried out, with a strongly positive calcium excretion and systemic response. Oöphorectomy was performed; the pain was relieved and she left the hospital on the 10th postoperative day.

Histologic examination of the ovaries showed cortical stromal hyperplasia (Fig. 2).

Adrenalectomy.

Indications and selection. Good results in some series have led to adrenalectomy early in the life history of the disease. Indications are a good response to previous castration and a good response to cortisone inhibition test. A high urinary Tzn estrogen after castration corroborates the estrogenicity of the adrenal gland.

Contraindications. Hepatic or cerebral metastases or pulmonary lymphangitic carcinomatosis are not helped.

Technical notes. Good preoperative preparation is essential, such as correction of anemia and tapping of pleural effusions. After removal, each gland should be inspected to check its completeness, and the adrenal bed searched for the presence of accessory adrenal tissue, which is present in 32 per cent of the cases. In 16 per cent these accessory glands contain both cortex and medulla.[79*]

Endocrine care. Cortisone, 100 mg., is given by mouth forty-eight and twenty-four hours preoperatively. On the day of operation, cortisone acetate, 100 mg. intramuscularly, is supplemented by an intravenous infusion of hydrocortisone continued during the operation. In the first two postoperative days, 100 mg. of cortisone acetate is given intramuscularly, and thereafter the hormone is administered in doses diminishing by 25 mg. every third day until the maintenance dose of 37.5 to 50 mg. per day is reached. This is supplemented with 0.1 mg. of fluorohydrocortisone per day for salt-retaining properties, which will obviate the need for added salt in the diet or administration of DOCA.

In the postoperative follow-up period, the patient must be impressed with the need to increase the cortisone dosage during periods of stress such as an infection or further surgery.

Results to be expected. In a series of 38 cases of metastatic breast cancer in women previously castrated, bilateral adrenalectomy produced objective remissions in 45 per cent.[35] Similar results are reported by Cade.[80] Sclerosis of bone lesions, disappearance of skin nodules, decrease in primary lesion and absorption of pleural effusions or ascites may all be seen. The subjective relief of bone pain may be dramatic. The duration of response is variable — rarely over two years.

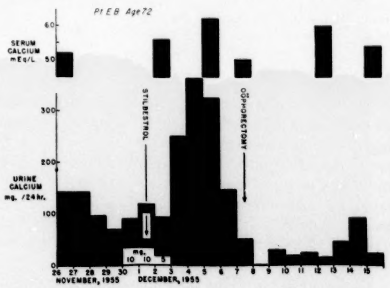


FIGURE 2. *Course in a Chronologically Elderly Woman, Twenty-three Years past the Menopause, Showing a Positive Response to Stilbestrol by Both Urine and Serum Calcium; There Was Minimal Aggravation of Symptoms. Oöphorectomy was followed by marked clinical improvement and a lowering of urine calcium excretion below the initial values.*

In a series of 8 cases we have failed to see such improvement. In 2 cases the progress of a slowly growing tumor was retarded. The remainder showed no improvement. In 1 case the growth rate and progress of the disease definitely increased; it is our interpretation — lacking proof — that in this case the removal of a source of adrenal estrogens may have decreased pituitary inhibition and allowed increased mammotrophic-hormone stimulation of the tumor.

The introduction of long-term cortisone treatment is surely a factor destined to confuse the evaluation of results after adrenalectomy and to change its indications.

The following case illustrates these problems.

D.A. (P.B.B.H. 8F912), a 44-year-old woman, underwent a radical mastectomy for carcinoma of the left breast in January, 1951. She remained well until September, 1953, when she manifested osseous metastases and received x-ray therapy to the right humerus and also methyl testosterone. Her periods were regular; she was nulliparous.

*Pearson et al.[35] believe that the accrued results of oöphorectomy and adrenalectomy will be improved when these operations are performed simultaneously.

She was admitted to the Peter Bent Brigham Hospital in March, 1954. Physical examination revealed no disease, but x-ray study showed new osteolytic lesions. A stilbestrol stimulation test was carried out, and a positive systemic response and rise in urine calcium obtained. Hysterectomy and oöphorectomy were performed, and a remission obtained that lasted for 15 months. Pain then developed in the right shoulder, ribs, pelvis and right thigh, and x-ray examination showed extension of osseous metastases.

Cortisone therapy was started, and symptomatic improvement obtained. She remained well and asymptomatic for 4 months, and further bone pain and x-ray evidence of increased skeletal spread then developed. It was thought that the beneficial effect of the cortisone therapy was wearing off, and a bilateral adrenalectomy was carried out.

She received no symptomatic relief from this procedure, and 6 weeks later was readmitted to the hospital for evaluation. Investigations showed that the spread and growth of the osseous metastases were occurring at an increased rate.

Hypophysectomy.

Indications and selections. No satisfactory method of selection is currently available. Patients responding well to gonadectomy and adrenalectomy may be expected to improve after hypophysectomy. There may be a group of patients whose tumors are stimulated by mammotrophic hormone alone, who will gain a remission from hypophysectomy when they have failed to show improvement after ovariectomy or adrenalectomy.

Technical notes. This operation requires the skill of an experienced neurosurgeon. It is performed through a right frontal craniotomy; the frontal lobe is elevated and retracted to obtain exposure of the sella turcica; the stalk is divided, and the pituitary gland removed. Completeness of removal is essential.

Endocrine care. Cortisone requirements are managed as described for bilateral adrenalectomy.

Thyroid will not be needed for six weeks, but after that time should be administered in a dosage of 0.09 to 0.2 gm. (1½ to 3 gr.) per day.

The development of diabetes insipidus after hypophysectomy is unpredictable. About 50 per cent of patients show no diabetes insipidus, but the remainder have symptoms of varying severity. Half of those in whom diabetes insipidus develops have daily urine volumes less than 4000 ml. and by increasing their fluid intake are able to live without requiring vasopressin (Pitressin). The remainder, with large urine volumes, require vasopressin tannate in oil. This may be supplemented between injections by inhalation in the form of snuff. Management of these patients and the adjustment of their vasopressin needs may not be a simple matter and must be completed satisfactorily before they leave the hospital.

We have been unable to confirm the belief of Ikkos, Luft and Olivecrona[81] that the increased solute load associated with cortisone therapy increases the vasopressin need and that the patient can be controlled on diminished vasopressin dosage if cortisone is withheld completely after the initial postoperative period.

Results to be expected. Pearson et al.,[43] reporting on 41 cases of breast cancer treated by hypophysectomy, showed objective improvement in 21; the remainder failed to respond. Eleven patients had had previous castration and adrenalectomy, and 5 of these showed a further good remission after hypophysectomy. Of 24 patients who had a primary hypophysectomy, 15 showed an objective improvement. Responses were seen in primary and secondary lesions. Similar results have been reported by Luft and Olivecrona.[82]

In a series of 10 cases of advanced mammary cancer treated by hypophysectomy* we have found objective and subjective improvement in 6 cases, the degree of improvement being marked in 2.

We believe that this relatively high ratio of success to failures is a reflection of attempted selection and that with improved technics of assaying mammotrophic-hormone activity[44] the accuracy of this selection may be further increased. The following case illustrates a fine result from hypophysectomy:

L.E. (P.B.B.H. 5H931), a 42-year-old woman, underwent radical mastectomy for carcinoma of the right breast in 1951. She remained well until October, 1953, when a recurrence in the scar was excised and a bilateral oöphorectomy carried out. Osseous metastases were demonstrated in November, 1954, and treated with radiotherapy.

She had 2 children, both breast fed for 6 months. She had received estrogen therapy throughout both pregnancies.

On admission to the Peter Bent Brigham Hospital in April, 1955, she had widespread osseous metastases and massive edema of the right arm, with active cutaneous metastases in the mastectomy wound.

An estrogen stimulation test produced a marked systemic response, with increase in turgor and growth of the cutaneous lesions. A symptomatic remission was achieved with cortisone therapy.

On June 29, 1955, hypophysectomy produced immediate symptomatic improvement as well as objective improvement seen in the decrease in edema of the arm and in the turgor and redness of cutaneous nodules. The remission has been maintained.

The following case illustrates a fine result from hypophysectomy in a male patient:

W.S. (P.B.B.H. 9G875), a 69-year-old man, underwent radical mastectomy for carcinoma of the left breast in 1950. He received local x-ray therapy after operation.

In 1952 a recurrence in the left axilla and supraclavicular area was treated with x-ray therapy.

In 1953 the diagnosis of osteolytic metastases of the spine was made, and a course of stilbestrol, 6 mg. per day, was started. He became asymptomatic and remained relatively well until November, 1954, when back pain increased and x-ray study revealed progress of the disease.

Orchiectomy was performed and produced a 3-month remission. In February, 1955, he was admitted to the hospital because of an exacerbation of the disease, and hypophysectomy was carried out, with immediate relief of bone pain.

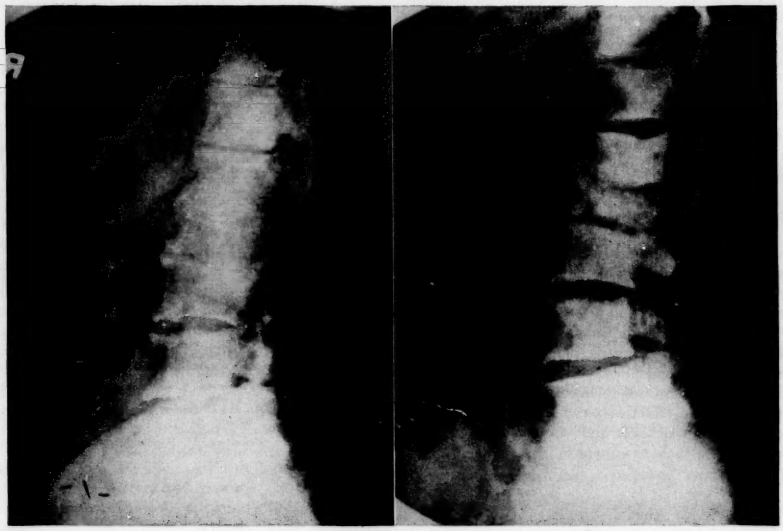
The osteolytic lesions have undergone sclerosis, and he remained well and asymptomatic 1 year after hypophysectomy (Fig. 3*A* and *B*).

Hypophysectomy does not share the potential fault of adrenalectomy — namely, a sudden upsurge of mammotrophic activity. The long-term management of patients after hypophysectomy is much simpler if their adrenal glands are still in place. For these reasons, as well as initial results, adrenalectomy may be expected to decline in the frequency of use, and hypophysectomy to increase.

*These operations have been performed by Dr. Donald D. Matson. Technic, management and detailed results are to be reported separately.

VI–Irradiation

It has been known for years that careful anatomic dissection, conscientious asepsis and a broad clinical and pathological orientation are prerequisites to good surgery in this disease. It is not so widely recognized —at least by surgeons and internists—that intelligent use of radiation requires an equal amount of professional preparation and experienced sagacity.



A B

FIGURE 3. *X-Ray Films in W.S., a Sixty-nine-Year-Old Man with Metastatic Cancer of the Breast, before* (A) *and Six Months after* (B) *Hypophysectomy.*
The adrenal glands had not been removed. Recalcification of the skeleton proceeded rapidly during a prolonged clinical arrest of the disease.

This section on irradiation is necessarily brief; our most important emphasis is on the absolute necessity that irradiation be carried out by an experienced radiologist with adequate equipment. Hasty, slovenly or ill advised irradiation is every bit as hazardous to these patients as inadequate surgery.

Irradiation to the Local Disease

When the primary tumor lies in the lateral half of the breast and has been grossly removed and pathological examination shows no involvement of the axillary lymph nodes, there is no indication for local irradiation. In all cases in which the lesion lies in the medial half of the breast the internal mammary nodes should be irradiated.

When axillary nodes are grossly involved simple mastectomy, if carried out, should be followed by careful irradiation (a suitable period for wound healing being allowed). When axillary involvement is found on pathological examination of axillary contents from radical mastectomy x-ray therapy should be given. In both the foregoing circumstances the irradiation should be directed to axillary, supraclavicular and internal mammary areas.

Irradiation of the Ovaries

Surgical castration can be carried out so easily and with such minimal trauma to the patient that it is scarcely ever contraindicated. One does, rarely, encounter patients with such widespread disease or such strong systemic contraindications that x-ray castration is advisable. This should be carried out with dosage adequate to prevent production of estrogenic substances by the ovaries as well as to produce cessation of the menses. It would be advisable for the radiologist conscientiously to determine the FSH values in the urine before and after x-ray treatment in young persons.

The following case illustrates certain problems that arise in x-ray castration:

M.B. (P.B.B.H. 8F427), a 41-year-old woman, was admitted to the Peter Bent Brigham Hospital in January, 1956. In 1951 she underwent a radical mastectomy on the left for carcinoma, which arose during a pregnancy that was not interrupted, and apart from the development of lymphedema she remained well.

In June, 1953, she received an x-ray castration (1150 r to the ovaries), after which her periods ceased and she had hot flashes. One year before admission, for a period of 2 months, she had a recurrence of these hot flashes. Six weeks before admission pain developed in the left jaw, and x-ray study of the skull revealed numerous osseous metastases.

She had 5 children, only 1 of whom was breast fed for a period of 6 weeks.

Examination revealed a young woman in good general health with no clinical evidence of recurrent disease. Investigations showed a serum calcium of 5 milliequiv. per liter, 24-hour urine calcium excretion of 60-70 mg. and urine estrogens, To 125 I.U., Tzn 670 I.U.

In view of the history suggesting continuing estrogenic activity and the presence of raised urinary estrogen levels, it was believed that x-ray castration, although producing amenorrhea, had not stopped ovarian estrogen secretion. Accordingly, surgical castration was performed. The ovaries were histologically normal.

Irradiation to Painful Areas of Metastatic Disease

Painful local areas of disease in the femur, the vertebras, the sacroiliac areas and many other portions of the skeleton can be most favorably influenced by accurately focused x-ray therapy. Such therapy, both in dose and in anatomic extent, may be sufficiently limited to obviate serious irradiation reaction, in terms of either radiation sickness or hematologic response. Most carcinoma of the breast is so radiosensitive that therapy of this type can be applied effectively with ordinary 250-KV equipment. The important thing is not the magnitude of the voltage, but the accuracy of objective planning of dosage and precision of anatomic localization.

Soft-tissue metastases to liver, lung and brain are very resistant to effective x-ray palliation. In addition, irradiation sickness and visceral damage often contraindicate such treatment.

When a patient is embarking on a long-term planned program of endocrine therapy, it may at times be advisable to withhold x-ray therapy to the symptomatic areas, these being used as additional helpful guides to the efficacy of systemic treatment. Under other circumstances there is no contraindication to carrying on the two simultaneously; in this way the patient may receive symptomatic benefit in a short period while long-term objectives are being met by endocrine measures.

(To be concluded)

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MEDICAL INTELLIGENCE

A STATISTICAL APPRAISAL OF THE SERUM PROTEIN-BOUND IODINE AS A TEST OF THYROID FUNCTION*

MORRIS E. DAILEY, M.D.,† AND
J. RICHARD SKAHEN, M.D.‡

SAN FRANCISCO AND OAKLAND, CALIFORNIA

THIS study was designed to ascertain the clinical usefulness of the serum protein-bound iodine as a gauge of thyroid function.

MATERIAL AND METHOD

For this purpose we reviewed the records of a group of consecutive patients seen in this clinic, in all of whom the levels of serum protein-bound iodine had been measured.§ Without knowledge of the levels reported, we classified each case as euthyroid, hypothyroid or hyperthyroid. Cases were not included if the clinician had failed to make an unequivocal statement regarding thyroid function, if the patient had taken organic iodine compounds (such as Lipiodol and Priodox) at any time or if any inorganic iodine had been taken within two months. None of these patients had any known endocrinopathy other than thyroid disorders. Patients known to be pregnant were also excluded, since the level of protein-bound iodine in such cases may be elevated.[2] To recapitulate, except for the protein-bound iodine, the clinician had available all clinical and laboratory evidence regarding thyroid function (basal metabolic rate in all cases, serum cholesterol level and uptake of radioactive iodine in doubtful cases).

The euthyroid cases were divided into the following subgroups:

Group 1 (Controls)

This group consisted of a total of 313 patients (63 men and 250 women), including several volunteers, without past or present evidence of thyroid dysfunction. Except for the volunteers, the serum protein-bound iodine had been tested because of unexplained tachycardia, leukemia, rheumatoid arthritis and, in a number of cases, "nervousness," but not of the degree or constancy to warrant a diagnosis of chronic-anxiety state.

Group 2 (Anxiety State)

Since it has been reported that thyroid function may be altered under chronic emotional stress,[3] 126 cases of anxiety state were tentatively placed in Group 2. In all cases the diagnosis had been established by competent psychiatrists. None of these patients had evidence of thyroid dysfunction.

Group 3 (Obesity)

This group was composed of 44 patients who were grossly overweight by the standard tables, and they too were tentatively excluded from the euthyroid group. Williams[4] reported that 11 of 24 comparably obese subjects had values for protein-bound iodine below 4.0 microgm. per 100 ml., but he concluded that hypothyroidism was probably only a minor factor.

Group 4 (Present Goiter)

This group consisted of 96 patients who had a readily palpable thyroid gland, considered to be definitely enlarged. Thyroiditis was not considered to be present in any of these patients; the majority were believed to have simple involutionary goiters.

Group 5 (Previous Thyroidectomy)

The 141 patients comprising this group had undergone thyroidectomy for a variety of types of goiter, including carcinoma.

Group 6 (Previous I^{131} Therapy)

These 49 patients had received radioactive iodine therapeutically for either Graves's disease or postoperative recurrence of that disease.

Group 7 (Current Treatment with Desiccated Thyroid)

This group of 35 patients required thyroid substance to remain euthyroid. The majority were receiving 0.1 gm. of *U.S.P.* thyroid substance daily.

The homogeneity of the controls (Group 1) for the possible influence of sex on the protein-bound iodine and the gross influence of age was studied. The mean and standard error of the levels in each sex were almost identical. Because Kountz and his associates[5] reported a decrease in thyroid function with age in males as judged by this test, we calculated the correlation coefficient, r, for age and level of protein-bound iodine of persons in Group 1. The low r value of −0.10 suggested that there was no correlation between age and level of protein-bound iodine.

The essential identity of the 7 subgroups can be appreciated by a study of the histograms of the popula-

*From the Department of Medicine, University of California School of Medicine, San Francisco, and the Veterans Administration Hospital, Oakland, California.

†Assistant clinical professor of medicine, University of California School of Medicine; present address, San Jose Clinic, San Jose, California.

‡Assistant chief of laboratory, Veterans Administration Hospital, Oakland, California.

§The method of Salter and McKay,[1] with minor modifications, is used for the determinations in this clinic.

tions concerned. Since statistical analysis established their homogeneity, the subgroups were combined, forming a total euthyroid group of 804 subjects (Fig. 1).

Results

Cumulative frequency distributions of concentrations for the euthyroid, hypothyroid and hyperthyroid groups are shown in Figure 2, together with the means and standard errors. In the euthyroid and hypothyroid groups the distribution is essentially normal, whereas in the hyperthyroid group it shows a distinct skew, as reflected by a standard error of 3.14 in comparison to the smaller standard errors of 1.49 and 1.10 for the euthyroid and hypothyroid groups, respectively. As can be expected with a biologic test, a considerable overlap of values was found in the extremes of the groups studied. The levels in the top 25 per cent of the hypothyroid group were equal to those in the lowest 25 per cent of the euthyroid group. Similarly, 55 per cent of the euthyroid group showed concentrations in the range of those found in the lower 25 per cent of the hyperthyroid group.

The significance of the differences of the means of the three groups was assessed. The *t* value found upon comparison of the mean levels of protein-bound iodine for the hyperthyroid and hypothyroid groups was 2.8, indicating that the difference in mean levels for these two groups was significant (1 per cent level). Comparison of the mean levels for the hyperthyroid and euthyroid groups yielded a *t* ratio of 1.98, indicating a difference significant at the 5 per cent level. The means for the hypothyroid and the euthyroid groups were not statistically different; the *t* value was 1.11.

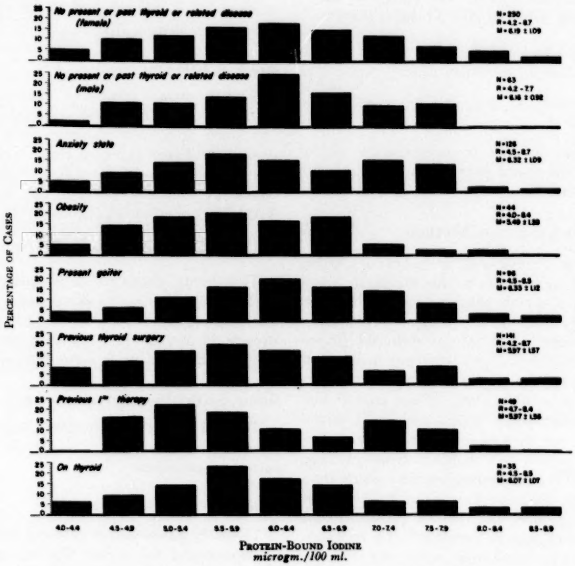

Figure 1. *Values for Serum Protein-Bound Iodine.*

Discussion

Despite the overlapping in the three groups, the determination of protein-bound iodine is of distinct diagnostic assistance when elevated levels are found. In such cases, provided that pregnancy, the acute phase of subacute thyroiditis or iodine contamination is absent, the diagnosis of hyperthyroidism is very likely. Indeed, if a value of 10 microgm. per 100 ml. is reported the likelihood that the subject is euthyroid is less than 1 in 100.

It is not the purpose of this report to compare the test with other laboratory means of assessing thyroid function. Other data from this clinic, however, indicate that an elevation of the I^{131} uptake by the thyroid gland correlates best with thyroid overactivity. The

basal metabolic rate is of primary value in assessing the *degree* of toxicity in hyperthyroidism; the other two tests seem to lack this quantitative aspect, except grossly.

The test of protein-bound iodine is of little value in the diagnosis of hypothyroidism if 4.0 microgm. per 100 ml. is accepted as the arbitrary lower limit of normal; lower values usually only confirm what is evident clinically. It may be true, however, as Starr[6] has emphasized, that clinical appreciation of low thyroid function is highly inaccurate and that many patients with "low-normal" levels of protein-bound iodine are indeed hypothyroid. Support is found for this view when alteration of the protein-bound iodine, basal metabolic rate and serum cholesterol from baseline levels is observed in patients in whom clinical hypothyroidism has developed after thyroidectomy for nontoxic goiters. For instance, the protein-bound iodine may drop 2 microgm. per 100 ml. from the preoperative value and yet still be within the accepted normal range. A trial of thyroid therapy is sometimes required to ascertain the true need for substitution therapy.[7]

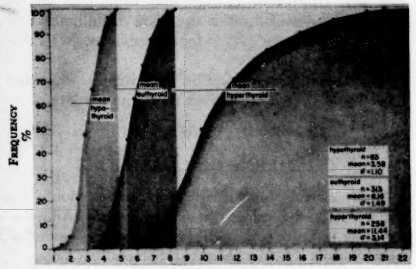

FIGURE 2. *Cumulative Frequency Distribution of Serum Protein-Bound Iodine.*

CONCLUSIONS

Statistical evaluation shows no significant difference between levels of protein-bound iodine of clinically euthyroid subjects, regardless of whether they are suffering from anxiety states, obesity or a nontoxic goiter, have had a thyroidectomy previously or previous I^{131} therapy for hyperthyroidism or are receiving therapeutic doses of desiccated thyroid substance for hypothyroidism.

The greatest value of the test is that elevated values of protein-bound iodine in the absence of pregnancy, thyroiditis or iodine medication make the diagnosis of hyperthyroidism highly probable.

With present clinical standards, perhaps inadequate, for the diagnosis of hypothyroidism, the determination will disclose few cases not suspected clinically.

Comparison of preoperative and postoperative values helps appraise thyroid function in patients who have undergone thyroidectomy for nontoxic goiter.

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SERMONS IN STONES —

HENRY JACKSON, JR., M.D.

TRYON, NORTH CAROLINA

NOT very long ago there was a little boy of thirteen summers in a small New England town. He looked to be about nine or ten. Though bright as a button, he was very short and at the age of thirteen he showed not the slightest evidence, either physically or emotionally, of sexual maturity. A local doctor full of whimsey and the latest "scientific" ideas, filled him with expensive medicines, no one of which could possibly make him grow. One of them could, quite easily, do considerable harm. No adequate family history had been taken in spite of the fact that certain physical and mental traits are well known to run in families. His mother was small; his father tall and powerful. His oldest brother was short and built after the fashion of a Polled Angus bull; to pat him was like patting an oak 4 x 4. His middle brother, aged seventeen, was tall, rangy and clearly had not reached his full growth or strength. His grandfather, like his father, was tall and powerful, as well as taciturn and stone deaf — when he wanted to be. And yet the small boy did not grow. Science, apparently, had failed.

And then, one day, along came a physician-friend of the family. He had thirty-five years' experience behind him, and excellent training in three of the best medical centers in the country, a love of humanity in general and of the small boy in particular. He remembered Francis Peabody's sage advice: ". . . the secret of the care of the patient is caring for the patient." He threw all the wonder drugs down the hopper and sat down with the middle brother —

alone. "Tell me, Paul, at thirteen were you very small?" "I was." "And when did you reach puberty?" "When I was sixteen." "And how was it, in this respect, with your older brother?" "The same." "Do you think your younger brother will grow up without the aid of expensive wonder drugs?" "I do."

The small boy's bone age was determined, at a medical center, to be that of a ten-year-old, if even that. In the past year he has grown so that his family is hard put to keep him in clothes and he has won a silver cup for a batting average of .575. This treatment or rather lack of it is the Art of Medicine — not the Science.

Many years ago an up-state Vermont doctor who used to make rounds with his father told this story. One night, in the dead of winter, they were called out to see a woman who was "powerful sick." Let the younger doctor tell it. "We drove out and there was the woman in bed. My father listened to her lungs and took her temperature and said, 'Now, Mary, you take one of these pills every three hours in a third of a glass of warm water and you'll be all right.' Then he went out to the kitchen, put his feet on the table and said, casual like, 'Well, John, how's things?' 'Well they ain't so good.' 'How's that?' 'One of my hosses is sick.' My father's feet hit the floor like a ton of brick. 'Let me look at him.' He went out to the barn and he looked in that hoss's eyes and in his mouth; he listened to his heart and his lungs; he felt of his belly and he looked up his tail. Then he said, 'John, get me a quart bottle and my hoss medicines.' He mixed up a dose, pried that hoss's mouth open and poured it down. 'Now, John,' he said, 'give that hoss all the water he wants but nothing to eat. He'll be all right in a day or so.' "

Here, too, the Art of Medicine — and its versatility — are exemplified.

Not long ago a physician was hospitalized for a mysterious ailment. Ten thousand times ten thousand tests were done and when they were all negative the patient and those in charge were bewildered, frustrated and unhappy. A month or so later, in another hospital, the situation was correctly appraised in fifteen minutes by a surgeon who had a heart of gold and knew his patients through and through. That is the Art of Medicine and it is dearly bought.

No one ever said — until later — "Never mind the diagnosis. That is simply a necessary and convenient label. Think, rather, how serious is this that you have? How will it affect your future and that of your friends? Think of what you really wish to do in the coming years. Assemble, as best you may, the assets and the liabilities that you have with which to carry out these plans. Do not be disturbed if it takes you a month or a year to come to a just conclusion. And remember that for the price of this room and all that goes with it, there can be had in Jamaica, or some such place, accommodations that will give you fishing and boating and swimming and that which you need most — happiness."

That is the philosophy of medicine as possessed by only a few in each generation.

Science of course is necessary; it has its justified place and each year it becomes more important to the proper practice of medicine. But neither tests nor science can fully replace the art of medicine and that is fast disappearing, though occasionally one sees shy, frightened bits peering cautiously out at the man who is ill through the maze of millimols and hydrogen ions and tests for histoplasmosis, which mean precisely nothing.

Two thousand years ago St. Paul wrote, "Physician heal thyself." It is almost but not quite too late.

CHAMPION OF CHAMPIONS

MANY of the *Journal's* readers are no doubt familiar with the career of Miss Tenley Albright, daughter of Dr. Hollis L. Albright, executive councilor from Suffolk District Medical Society.

MISS TENLEY ALBRIGHT

The accompanying picture of Miss Albright, twice world figure-skating champion and current Olympic and national champion, is inscribed as an expression of the esteem in which she holds her own physician, now president of the Massachusetts Medical Society. Tenley's fame is on ice; her charm is a constant phenomenon.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42191

PRESENTATION OF CASE

A fifty-five-year-old housewife entered the hospital because of an abdominal mass.

For three or four years previously she had noted a progressively enlarging mass in the lower right side of the abdomen. About five weeks before entry she had malaise, chills and diarrhea with intermittent, nonradiating pain in the upper abdomen that usually occurred before, but occasionally after, meals, and subsequently subsided.

Two years before admission an adenoma of the right parotid gland was excised.

Physical examination showed an obese woman. Examination of the chest was negative. Abdominal examination revealed a rounded, firm, freely movable, nonfluctuant, nontender mass measuring 5 cm. in diameter in the right lower quadrant. The mass did not move with respiration. The liver and spleen were not felt. Pelvic examination revealed a hard cervix, with erosion of the mucosa and healed lateral lacerations; the uterine fundus and adnexa were normal; there was a moderate cystocele and rectocele. Rectal examination was negative.

The temperature was 99.2°F., the pulse 84, and the respirations 20. The blood pressure was 124 systolic, 80 diastolic.

The urinary sediment contained 20 white cells per high-power field. Examination of the blood revealed a hemoglobin of 13.6 gm. per 100 ml. and a white-cell count of 9200. The nonprotein nitrogen was 27 mg., the total protein 7.1 gm., the albumin 4.7 gm., the globulin 2.4 gm., and the fasting blood sugar 110 mg. per 100 ml. Numerous stool specimens were normal in color and each gave a ++ guaiac test. X-ray films of the chest showed elevation of the lateral portion of the right hemidiaphragm and blunting of the right costophrenic angle. Barium-enema examination demonstrated a crescentic filling defect measuring 4.5 cm. in diameter in the cecum (Fig. 1); the border of this defect was smooth except for irregular barium streaking in its superior portion; there was a probable soft-tissue mass extending from the region of the filling defect to beyond the wall of the cecum. Sigmoidoscopic examination was negative. Biopsy of the cervix showed acute and chronic cervicitis. Cytologic examination of a vaginal smear was negative for malignant cells.

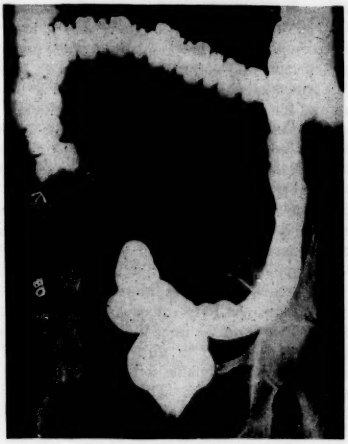

FIGURE 1. *Film from the Barium-Enema Examination, Showing a Smooth Defect at the Tip of the Cecum (Arrows).*

An operation was performed on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI*: Before concentrating on the mass in the right lower quadrant, I shall try to eliminate data that I believe are "red herrings." One is the adenoma of the parotid gland. Adenoma of the parotid gland is extremely rare; it is more likely that the mass was really a mixed tumor of the parotid gland. If it was a mixed tumor, could it have been malignant and have metastasized to the wall of the cecum? Although malignant mixed tumors of the parotid gland can metastasize to unusual sites, I think that this would be very unusual; therefore, I shall dismiss the mass in the parotid gland as not relevant to the abdominal condition. The other "red herring" is the films of the chest, which show blunting of the costophrenic angle. That is seen in the lateral aspect of the chest posteriorly where the right

*Chief, Department of Radiology, Mount Auburn Hospital, Cambridge, Massachusetts.

leaf of the diaphragm is not down as far as it should be. Could this conceivably be caused by fluid trapped there? No films with the patient in a horizontal position were included so that I do not know whether this shadow changed in position; I assume, for the purpose of the conference, that it did not and that it was an old process in the pleura rather than a recent effusion. If it were effusion it would be significant.

Over the course of two to four years a mass developed in the right lower quadrant; the mass was freely movable and nontender, and produced changes in the x-ray appearance of the cecum (Fig. 1). It is natural for me to concentrate on this finding. The defect is crescentic; probably it is better to say that there is a lesion with a smooth, semioval upper edge that nearly amputates the tip of the cecum. The finding is visible on all the films; on the large films the upper edge looks smooth. One spot film, at which I glanced and which I planned to study carefully later, I unfortunately mislaid. I am very unhappy about that and apologize to the hospital. I am particularly unhappy because the glance showed me that it was an interesting film. As I remember it, the defect did not appear as it does on the large films but was somewhat lobulated and seemed to turn a little on itself. I cannot see the questionable soft-tissue mass that was mentioned in the report. The terminal ileum close to the defect, however, is slightly displaced medially, probably by the mass. No calcification is visible in the region of the defect. There are two tiny air pockets visible: one near the cecum and one higher up. I assume that they are without significance since they shift in position. One is probably within the small bowel; the one in the region of the liver is probably not an abscess cavity, but in an unusually high hepatic flexure.

There are numerous lesions that could give this roentgenologic appearance and a fair number that could give the combination of this roentgenologic appearance and the clinical story. One can classify them in the following groups: inflammatory mass such as an appendiceal abscess, mucocele of the appendix and tumor originating either in the appendix or in the tip of the cecum. A tumor may have arisen from the mucosa or from the wall below the mucosa and could have been benign or malignant. I shall try to determine which of the three is the best possibility.

In favor of the appendiceal abscess is the episode that took place about five weeks before entry during which the patient had chills, diarrhea and malaise. On admission there was a very slight elevation of temperature and a normal white-cell count. Against an appendiceal abscess are the absence of a calcified fecalith and the preserved retroperitoneal fat line clearly visible in the x-ray films, and the fact that the mass was freely movable and was markedly lobulated. An appendiceal abscess may be lobulated, but, as I recall, on the spot films, which I do not have, there was more lobulation than an appendiceal abscess usually has. The free mobility is not absolutely against an appendiceal abscess. Even the long duration and the mild clinical course are not against it, but the other findings, particularly the roentgenologic ones, make me think that this is the least likely of the possibilities that I have mentioned.

A mucocele of the appendix can produce the roentgenologic and clinical features of a gradually growing mass in the right lower quadrant with minimal clinical findings. Somewhat against a mucocele is the marked lobulation. The so-called chills, if they were chills and were related to the mass, are against mucocele. The bleeding, if the ++ guaiac test was significant, would be unusual for mucocele. A mucocele is a definite possibility.

The most common tumor in this region, with a long story, is carcinoid of the appendix. The radiologic picture is consistent with such a tumor. There is little in the clinical story against it. The chills that the patient may have had would not make me eliminate carcinoid. Blood in the stool only rarely occurs in carcinoid. Carcinoid, I believe, is a good possibility.

Of the tumors arising from the wall of the bowel below the mucosa, the most common is the submucosal lipoma of the bowel, which could definitely give this history and may occasionally bleed. Two things against this diagnosis are that the mass was much more lobulated than the usual lipoma is, although I have seen some that were quite lobulated, and, more important, that the mass was hard and had no "give" to it. As a matter of fact it would be somewhat unusual to be able to palpate a lipoma of that size through the abdominal wall with the ease with which this mass apparently was felt. I shall exclude the possibility of lipoma. The other intramural, extramucosal tumors, such as leiomyoma, are so extremely rare in this particular site that I shall exclude them although they can give this appearance radiologically.

One possibility remaining is cancer of the tip of the cecum. The x-ray appearance could be produced by a cancer of the tip of the cecum. The clinical picture and the findings on examination of the patient are perfectly consistent with cancer. The only serious objection to such a diagnosis is the history of tumor growing slowly over a period of three to four years, but I am not willing to accept the long-standing history as excluding the possibility of cancer completely. We know that cancer of the colon can grow slowly. I have seen films of a patient that I unfortunately called normal. Three years later the patient had a cancer. When I reviewed the original films, I could find a small lesion in the colon so that I know that cancer of the colon can grow slowly over many years. This is a definite possibility.

Of the three possibilities — carcinoid, mucocele and cancer — I shall put carcinoid first, cancer second and mucocele third.

DR. EDWARD D. CHURCHILL: Would a tumor of the right ovary do this?

DR. SCHATZKI: Yes, but I do not believe it could produce a freely movable tumor.

DR. CHURCHILL: I cannot tempt you into a Meigs syndrome!

DR. SCHATZKI: I thought of that when I first saw the films but excluded it because of the free mobility of the tumor with the cecum.

A PHYSICIAN: Is a chronic intussusception a possibility?

DR. SCHATZKI: That is excluded by the location of the mass below the ileocecal valve.

A PHYSICIAN: Can you locate the position of the mass?

DR. SCHATZKI: Yes; it is in the cecum lateral to the terminal ileum.

A PHYSICIAN: Would you consider chronic diverticulitis of the right side of the colon?

DR. SCHATZKI: I should classify that in the same group with appendiceal abscess, — an abscess caused either by appendicitis or by isolated diverticulitis, — and for the reasons I mentioned I thought that that was less likely than the other possibilities.

A PHYSICIAN: Would you consider a granulomatous lesion?

DR. SCHATZKI: That is unlikely for two reasons: one is the complete absence of any irritation of the cecum, and the other that, although the mass was somewhat lobulated, it had a smooth surface.

DR. C. C. WANG: Do you see any destruction of the mucosal folds to suggest a diagnosis of carcinoma?

DR. SCHATZKI: I cannot, on these films; I do not recall its appearance on the spot films.

DR. WANG: I saw the spot films and thought that the mass looked like an intramural, extramucosal lesion.

DR. SCHATZKI: Did it have the tiny hook that I mentioned?

DR. WANG: Yes; it looked to me as though a mass were indenting the cecum instead of arising from it.

DR. SCHATZKI: I do not believe that one can differentiate that radiologically. This is why I said all these conditions that I have mentioned can give the same radiologic appearance. They have such completely different origins that this statement must sound unbelievable to the clinician. There is no principal radiologic difference in the appearance of a lesion that arises from the mucosa, a lesion that arises from the wall below the mucosa and a lesion that arises outside the intestinal tract but has become attached solidly to the wall of the intestine, for they all may overhang or protrude. The only one that can be differentiated by its completely different appearance roentgenologically is the unattached extrinsic lesion. The way in which we may be able to differentiate the other three possibilities is by means of our knowledge of gross pathologic anatomy. The lesions that arise in the mucosa and those that arise below it in the wall have at times different shapes and a different gross appearance.

A PHYSICIAN: Could this have been a sessile polyp?

DR. SCHATZKI: I should consider that to be in the group of cancers. A simple polyp could not be palpated through the abdominal wall by the patient for three years. I think a polypoid carcinoma could give this picture.

DR. BENJAMIN CASTLEMAN: A sessile polyp that had intussuscepted could produce this picture.

DR. SCHATZKI: Yes; however, there is no intussusception through the ileocecal valve. The tip of the cecum can intussuscept on itself — and frequently does with submucous lipomas of that area; the cecum, like a finger of the glove, first becomes indented and then intussuscepts. If there was intussusception in this case it was so short that it did not manifest itself on the films.

CLINICAL DIAGNOSIS

Carcinoma of cecum.

DR. RICHARD SCHATZKI'S DIAGNOSIS

Carcinoid of appendix.
? Carcinoma of cecum.
? Mucocele of appendix.

ANATOMICAL DIAGNOSIS

Mucocele of appendix.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The diagnosis before operation was cancer of the cecum. I am sorry that the surgeon is not here; his operative note indicates clearly what the lesion was. He described the lesion as a 5-cm., rounded, smooth polyp within the cecum, which on palpation from the outside appeared to communicate with an appendix dilated to about 3 cm. in diameter. The appendix lay posterior to the cecum, retrocecally, and seemed to contain a mucoid fluid within it. Pressure on the appendix was transmitted to the mass within the cecum, which was believed to be an extension of an appendiceal cyst or a mucocele. The surgeon, after partially immobilizing the cecum, made a transverse incision over the lowermost portion of it through the serosa and muscularis, but not into the mucosa, and excised the cystic extension of the appendix, without entering the cecum. There was no obstruction to the ileocecal valve as the result of this procedure. The specimen received in the laboratory was a very large mucocele of the appendix, part of which had herniated into the cecum to give the lobulated appearance seen on x-ray examination. It must have been under great pressure because it had

produced a little pocket that apparently pushed into the cecum. We were unable to find any stricture that might have been the basis for the mucocele; the surgeon's clamp may have obscured one.

A PHYSICIAN: Were the pathological findings consistent with the repeatedly positive guaiac tests on the stools?

DR. CASTLEMAN: The thin mucosa over the part of the mucocele that bulged into the cecum may have bled at times.

CASE 42192

PRESENTATION OF CASE

An eighty-one-year-old woman was admitted to the hospital because of jaundice.

Four or five weeks previously she noted anorexia and fatigue. About one week later the urine was dark, and the stools light. At the same time there was postprandial vomiting of bitter-tasting material. There were also abdominal "gas" cramps that were relieved by bowel movements. Two weeks before admission slight pruritus was noted, and her physician told her that she was jaundiced. During the two weeks before entry the stools appeared normal, and the urine was less dark. She had lost 20 pounds in weight in the two months before admission. There were no chills or fever and no exposure to rats, hepatotoxins or jaundiced persons. There was no history of alcoholism.

Physical examination revealed an obese, deeply jaundiced woman with scattered purpuric areas in the skin. There was a Grade 3, aortic, systolic murmur that was transmitted to the neck and apex. The liver edge, which was tender and questionably irregular, was palpable 4 fingerbreadths below the right costal margin. One observer felt an ill defined, hard, nodular mass in the left upper quadrant. The spleen was not palpable. There was no abdominal fluid wave.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine gave a ++ test for albumin and a ++++ test for bile; the sediment contained 20 to 40 white cells and an occasional granular cast per high-power field; two cultures showed no growth. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 ml. and a white-cell count of 10,200. The nonprotein nitrogen was 30 mg., the total protein 6.7 gm., the albumin 2.5 gm., the globulin 4.2 gm., the fasting blood glucose 89 mg., the serum bilirubin 19.5 mg. direct and 29.5 mg. total, the serum cholesterol 181 mg., and the cholesterol esters 32 mg. per 100 ml. The sodium was 139 milliequiv., the potassium 3 milliequiv., the chloride 100 milliequiv., and the carbon dioxide 29 milliequiv. per liter. The alkaline phosphatase was 12.9 units, and the prothrombin content 21 per cent. The cephalin flocculation was ++++ in forty-eight hours, and the thymol turbidity 13 units with ++ flocculation. The serum amylase was 11 Russell units, and the lipase 1 unit. The serum electrophoretic pattern showed a very large, diffuse gamma-globulin spot. A blood Hinton test was negative. Cytologic examination of gastric fluid for malignant cells was negative. X-ray films of the chest and abdomen and an upper gastrointestinal series were normal except for marked degenerative changes in the lumbar spine. Numerous stool specimens were light tan and gave a negative guaiac test. Vomitus gave a negative guaiac test; the pH was 4.5 and 6.5.

The patient continued to vomit. Therapy included a high-calorie, low-fat diet and Hykinone. On the second hospital day the urinary sediment contained numerous hyaline cellular and granular casts. From the fifth to the eighth hospital day vaginal bleeding was noted. Pelvic examination showed blood-tinged mucus coming from the endocervical canal. Cytologic examination of a vaginal smear for malignant cells was unsatisfactory. The patient slowly deteriorated, with increasing lethargy and weakness. She suddenly became hypotensive on the ninth hospital day, when physical examination showed her to be very weak, but oriented and able to respond to commands. The eyes roved from side to side. The pupils were constricted but reacted to light. A "liver flap" was present. The cardiac rate was regular and ranged between 40 and 52. Examination of the abdomen showed considerable ascites. The temperature was normal, the pulse 40 to 52 and regular, and the respirations 16. The blood pressure was 70 systolic, 40 diastolic. The serum nonprotein nitrogen was 77 mg., and the bilirubin 33 mg. per 100 ml. The serum sodium was 125 milliequiv., the chloride 87 milliequiv., the potassium 4.3 milliequiv., and the carbon dioxide 25 milliequiv. per liter. The blood ammonia was normal. An electrocardiogram showed a probable nodal pacemaker at a rate of 50; the QRS interval was 0.11 second; the axis was normal; there were no visible P waves; the T waves were low, with slight inversion, in Lead 3. Hydrocortisone given intravenously failed to produce any improvement. With Levophed the blood pressure was maintained at 110 systolic, although by the next day the patient was confused and disoriented, with Cheyne–Stokes respirations. The cardiac rate remained at about 50. She became oliguric and finally anuric. An abdominal paracentesis yielded 50 ml. of cloudy, bile-stained fluid that contained 8000 red cells and 500 white cells, with 80 per cent mononuclear cells and 20 per cent neutrophils per cubic millimeter; a smear showed many mesothelial cells; the total protein was 1.6 gm. per 100 ml.; culture was negative. She died on the eleventh hospital day.

Differential Diagnosis

Dr. Chester M. Jones*: The patient seems to have died of hepatic failure; possibly hemorrhage was a late precipitating factor, but there was no evidence for that except that she went into shock. She had been jaundiced for about seven weeks before liver failure occurred. As far as one can tell from the history she had had no other symptoms except a loss of 20 pounds in weight without obvious reasons in the preceding two months.

Dr. Austin L. Vickery: The weight decreased from 200 pounds to 180 pounds so that she was not exactly depleted.

Dr. Jones: On physical examination the patient was obese, which may have made it difficult to do an adequate examination. The examiner noted jaundice, purpura (which is important), cardiac signs, which I think had little or nothing to do with the final diagnosis, and a liver that was probably nodular and was 4 fingerbreadths below the costal margin. I think one would do well to demonstrate a nodular liver in a woman of this size.

Dr. Warren Point: The edge of the liver seemed smooth to me.

Dr. Jones: The liver edge was thought by one person to be nodular. The apparent nodularity could have been due to loss of subcutaneous fat with irregular areas of subcutaneous tissue. I think if we looked back through the clinicopathological cases, we would find that the statements that livers were or were not nodular had about an even chance of being correct.

Dr. Vickery: It is often difficult in abstracting a record to know whose clinical impression to select.

Dr. Jones: In addition there is the statement that an observer felt an ill defined, hard, nodular mass in the left upper quadrant. That is important information if it is correct. It could, of course, have been in the colon, and could have been simply fecal material, or it could have been in the pancreas. Another fact that one cannot overstress is that nobody felt the spleen. If the spleen had been palpable, it would help to clarify the picture because a palpable spleen with this sort of picture should imply intrahepatic disease. The purpura may well have been due to liver failure with a low prothrombin content, which was actually decreased to 20 per cent.

The urine showed the findings that one would expect in a patient with deep jaundice and, I think, had no diagnostic significance. The hemoglobin was almost normal for a woman of eighty-one years. There may have been hemoconcentration, and the true hemoglobin level may have been lower. The white-cell count was elevated somewhat, — at least it was not low, — I think that is important. If there had been cirrhosis without striking hepatic necrosis or without massive bleeding, the white-cell count would have been low rather than normal or high normal. The rest of the laboratory data are those of hepatic failure: low albumin, high globulin and high bilirubin. The patient did not have enough hemolysis to give much evidence of a striking anemia, and I doubt if an important portion of the elevation of bilirubin was on the basis of a blood dyscrasia. That the cholesterol esters were amazingly low tends to make me believe that the liver was functioning poorly, and the low prothrombin content confirms that impression. The elevated alkaline phosphatase suggests biliary obstruction. There was no evidence of bone disease except the osteoporosis, which is not unusual in a woman of eighty-one years. Therefore, a highly reasonable possibility for the elevated phosphatase is extrahepatic biliary obstruction. The flocculation tests were obviously abnormal. All the tests indicated severe interference with hepatic function. That is further substantiated by the high level of gamma globulin noted on electrophoresis.

I think that there is sufficient reason to postulate that the patient had chronic liver disease — I shall call it cirrhosis, which is another way of saying chronic liver disease. There are two possible explanations for this degree of hepatic failure with a large liver. One is a necrotizing process; however, a terminal acute yellow atrophy superimposed on hepatitis would be unusual at this age. The other, a rare situation, is almost complete replacement of the liver by a cancerous process.

There were some negative findings that are important. There was no evidence of neoplasm in the upper gastrointestinal tract and no evidence of metastatic disease in the lungs on the basis of the x-ray films. Unless the films show something not mentioned in the protocol I see no reason for examining them.

Dr. Joseph Hanelin: I agree; there may have been some ascites when she was first admitted.

Dr. Jones: There has to be a certain amount of ascites before it can be demonstrated by palpation; she may have had ascites at that time.

If one accepts the suggestion that there was no evidence of intrinsic disease in the upper digestive tract and no evidence of external pressure on the stomach, duodenum or first portion of the jejunum, one has valuable evidence against an initial neoplasm that arose in the stomach, in the esophagus or in the pancreas, causing pressure on the common duct or metastases to the liver. There was no barium-enema examination of the colon. That would have been desirable; if the patient had not been so sick I am sure it would have been done. Numerous stool specimens contained no occult blood. The absence of occult blood does not rule out carcinoma or other malignant conditions in the colon, but is evidence against it provided that no demonstrable metastatic disease is traceable to such a neoplasm.

*Physician, Massachusetts General Hospital.

Another finding, about which I can only speculate, is the bleeding from the vagina or cervix that apparently occurred shortly after admission. It had not been present before hospitalization. There was not a demonstrable uterine, endometrial or ovarian tumor. The pelvic examination does not rule out those possibilities but is strong evidence against them. The bleeding may have been the result of a low prothrombin content and the tendency to bleeding in a patient with obvious liver disease. No conclusions can be drawn from an unsatisfactory vaginal smear.

Two days before death the patient suddenly became hypotensive; one wonders whether there had been bleeding. There was no evidence of bleeding shortly before death. An abdominal paracentesis yielded fluid that contained at least 8000 red cells per cubic millimeter, which is not a tremendous number. Some of the blood may not have been the result of trauma but of free bleeding into the peritoneal cavity. It is difficult for me to believe that hepatic failure of this degree could be caused solely by a malignant process, but I believe that such a process was present. I wonder where the carcinoma could have been. She could have had carcinoma of the pancreas, with metastases to the liver, chronic liver disease with a superimposed hepatoma or even a cholangioma. Hepatoma occurs more frequently in men; cholangioma, which is rare, occurs more frequently in women. She had been asymptomatic until several weeks before she died. She may have had chronic liver disease that was asymptomatic and metastases from carcinoma of the colon. I have seen more than one tiny nodule of carcinoma in the colon that was found only at autopsy and yet the liver was replaced by carcinoma. I do not believe that she had uterine disease or carcinoma of the endometrium or of any genital organ with metastases to the liver. Such carcinomas are very rare, and I do not think they are logical explanations for this picture.

I think that this patient had an old, asymptomatic cirrhosis and metastatic carcinoma, probably from the digestive tract to the liver. A second choice would be an unusual and rapidly progressive infectious hepatitis lasting seven weeks and resulting in hepatic failure. I am sure that this happens, and yet it seems to me it is not as logical an explanation as the first.

One other question, Were gallstones found? A woman of this age has a 30 to 40 per cent chance of having them. She had no symptoms that would lead me to such a conclusion; therefore, I think that on the basis of the evidence it is an illogical diagnosis.

DR. VICKERY: Dr. Gabuzda, you saw this patient; will you tell us what the opinion on the ward was?

DR. THOMAS GABUZDA: At first we thought this was the classic history for carcinoma of the pancreas, but the reports of the liver-function tests confused the situation and made us consider a chronic cirrhosis, which was progressing, and more probably an infectious hepatitis. Finally, we became convinced that it was a combination of the possibilities that Dr. Jones mentioned.

DR. VICKERY: I noticed on the discharge form that the diagnoses were question of acute yellow atrophy, question of cirrhosis and question of acute myocardial infarction.

DR. GABUZDA: We were interested in the cardiac abnormality — primarily, the hypotension. The cardiac rate was as low as 40 and associated with hypotension; we wondered whether something had happened.

DR. JONES: I neglected to mention the nodal rhythm of the heart, but that may simply have been a reflection of the whole picture of hypotension and extreme depletion rather than anything more specific.

DR. POINT: I was asked to see the patient for a question of needle biopsy of the liver two days before she died. At that time there was no point to the biopsy, for it would not have helped the situation. As Dr. Gabuzda said, when she first entered the hospital, she had the typical appearance of a patient with obstruction and carcinoma of the pancreas. Do you suppose obstruction could have accounted for the whole picture?

DR. JONES: It would be quite unusual for the bilirubin to be this high from liver disease per se, and ordinarily obstruction alone would not produce this figure in such a relatively short time.

DR. POINT: It seemed at the time that the high bilirubin was evidence of underlying liver disease on which hepatoma had developed.

DR. JONES: Or possibly metastatic cancer.

DR. GABUZDA: The history is not quite clear about the abdominal mass; on entry one observer felt a mass in the left upper quadrant. On the next day other physicians agreed that there was a mass, but the majority of the observers thought that it was the left lobe of the liver or a mass continuous with the liver. Most physicians believed that there was a mass but could not agree about what it was.

DR. JACOB LERMAN: I should like to suggest that the bleeding from the cervical canal was produced by hyperplasia of the endometrium in a patient who had long-standing liver disease.

DR. JONES: This is quite possible, but I should think that at the age of eighty-one the estrogen level would be extremely low. Although the estrogen level may be increased in women with chronic liver disease after the menopause, it seems to me that she was too old. We do have vaginal smears from quite a few cirrhotic patients after the menopause that still show cornified cells.

DR. LERMAN: I have seen hyperplasia of the endometrium at seventy; I have not yet seen it in the eighties.

DR. JONES: I think that the bleeding could be explained by the low prothrombin content.

Clinical Diagnoses

? Acute yellow atrophy.
Portal cirrhosis of liver.
? Myocardial infarction, acute.

Dr. Chester M. Jones's Diagnoses

Metastatic carcinoma of liver.
Chronic cirrhosis of liver.

Anatomical Diagnoses

Adenocarcinoma of head of pancreas, with metastases to omentum and appendix.
Bile stasis of liver, severe, with focal necrosis.
Ascites.
Bile nephrosis.

Pathological Discussion

Dr. Vickery: At autopsy, the patient was obese and deeply jaundiced, and there were numerous ecchymoses over the skin. The abdomen contained 3000 ml. of clear, jaundice-colored fluid. Apparently, we shall have to assume that the blood in the paracentesis fluid removed was traumatic. The liver was not enlarged, weighing 1360 gm., and extended only 3 cm. below the right costal margin. Its surface was dark green, only faintly finely granular and not nodular. Its consistence was normal, and grossly, on cut section, there was no evidence of tumor or other distinguishing abnormal characteristics. The gall bladder contained mucinous white material and no calculi. Examination of the extrahepatic biliary tree was negative, except for a stone impacted in the cystic duct, accounting for the "white bile" in the gall bladder. However, the distal end of the common duct was markedly compressed by a firm head of the pancreas. Although the head of the pancreas did not contain a distinct mass, it presented a diffusely firm, fibrous consistence, which on microscopical section proved to be a diffusely infiltrating adenocarcinoma. There was massive metastasis to the omentum in the region of the splenic flexure, producing an ill defined mass, as referred to by Dr. Gabuzda. The only other tumor spread was a small solitary metastasis to the tip of the appendix.

The liver histologically was of particular interest because we also attempted to reconcile the laboratory data with an appropriate histologic picture of severe hepatocellular damage or massive replacement by tumor. Unfortunately, however, we are somewhat at a loss to explain the profound alterations in the liver-function tests on the histologic findings. The bile canaliculi were choked with thrombi of bile, but by and large the liver cells per se were intact except for focal zones of chronic inflammation and necrosis that were probably related to the prolonged obstructive jaundice. There was no evidence of extensive cellular damage in any area. Consequently, we were forced to conclude that the only disease in the liver was attributable to the severe bile stasis, secondary to obstruction.

The endometrium showed some activity and was cystic, which together with the bleeding tendency, as Dr. Jones mentioned, probably accounted for the vaginal bleeding. However, it did not exhibit the degree of hyperplasia sometimes observed with the relative hyperestrinism of chronic, severe liver disease. The heart examination was not remarkable, except for a fairly marked degree of calcification of the annulus of the mitral and aortic valves, relatable to arteriosclerosis. The only other finding of interest was in the kidneys, which showed nephrosclerosis, a condition that one might expect at the age of eighty, but in addition there was marked bile staining with many of the tubules plugged with bile casts, producing the microscopical picture known as bile nephrosis. This condition is not infrequently associated with serious renal impairment in severely jaundiced patients and is responsible for terminal uremia.

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FORD FOUNDATION TO THE FORE AGAIN

ONE can hardly say too much in appreciation of the enlightened generosity with which the trustees of the Ford Foundation have looked upon education in general and medical education in particular. Their allocation to general education last December not only was the greatest monetary gift in history but also included an appropriation of $90,000,000 to help the privately supported medical schools strengthen their own programs of instruction.

And now, within recent weeks, has come a new Ford Foundation appropriation of $10,000,000 directly to the National Fund for Medical Education, toward the unrestricted revenue of all the schools, both private and tax supported. The appropriation, however, is not a handout. It is rather a substantial prod; a reminder that the proper cultivation of the right talents will attract other talents in return; a priming of the pump; the injecting of a suitable substance into the cylinders to make the resulting explosions more powerful if no noisier.

Grants from this latest appropriation are to be disbursed on a matching scale in a program that will last from five to ten years, depending on the success that the Fund, now nearly seven years old, has in developing other sources of pecuniary supply. The largest amount that will be granted in a single year will be $2,000,000.

According to the formula that has been decided upon, if the Fund's receipts in 1956 equal the $2,147,000 raised in 1955 the Foundation's grant will equal 70 per cent of this amount, or $1,503,486. Any excess over the 1955 total will be matched dollar for dollar, up to a maximum of $2,000,000 for any one year; at the most rapid rate of disbursement the appropriation will therefore require the minimum five years for its expenditure. The matching of receipts will be on a diminishing scale in succeeding years although still dollar for dollar for any year's increase, up to the $2,000,000 ceiling.

The hope of the Foundation, under such a money-matching, pump-priming program, is that the National Fund, started in 1949 under such weighty auspices as were then invoked, will be assisted in its purpose of stimulating "the interest and response of the medical profession and of the general public, to the end that financial support for medical schools can be maintained at a level consistent with sound medical education."

Slowly the larger industries are becoming aware of the degree to which their own prosperity and proper functioning is dependent on the general welfare of the nation aside from the mere matter of financial well-being. Fortunately, such great forward-looking philanthropies as the Ford Foundation and the Commonwealth Fund already know of the crisis that confronts medical education and the effect that the

failure of medical education would have on the country as a whole.

The profession itself is making an increasingly substantial annual contribution to the Fund, through the American Medical Education Foundation and the alumni associations of the various schools.

HARRY M. HOXSEY

On April 4 the Food and Drug Administration issued a public release warning that the so-called Hoxsey treatment for internal cancer has been found by the United States Court of Appeals for the Fifth Circuit (on the basis of evidence presented by the Food and Drug Administration) to be worthless. This is only the beginning of another round of a long battle between the Food and Drug Administration and Harry M. Hoxsey, whose Cancer Clinics in Dallas, Texas and Portage, Pennsylvania, are doing a land-office business peddling cancer cures at $400 a treatment.

The Food and Drug Administration is starting off this round with a solid punch that may be the eventual undoing of an unquestionably formidable opponent. For Mr. Hoxsey (pronounced for descriptive purposes with a long o), backed by the ignorance and fear of a troubled people, has been blithely and successfully selling his wares and publicly ignoring an injunctive decree enjoining him or his agents from shipping his "cures" in interstate commerce with any labeling suggesting or representing that they were effective in the treatment of cancer.

The Food and Drug Administration is legally empowered to issue such public warnings. The fact that the warnings are made only in extreme cases and the current official warning is the first concerning cancer cures indicates the Government considers it high time to use radical treatment to cure the Texas cancer and its evident metastasis.

Because of the extensive promotions of the clinics, the public probably knows more about Harry Hoxsey than the medical profession does, although he has been selling cancer medicines for at least thirty years.

The often convicted Hoxsey (unlawful treatment of human ailments) set up his Cancer Clinic in Dallas, Texas, in 1936, and its growth has been steady since that time. The Portage, Pennsylvania, Clinic opened in March, 1955, with State Senator John J. Haluska, of Upper Pennsylvania, as its administrator. The Texas Clinic is staffed with 6, and the Portage Clinic with 2 osteopathic physicians.

According to the Food and Drug Administration, the individual Hoxsey treatment begins with a superficial and inadequate examination of the patient. Before November, 1954, the treatment consisted essentially of the administration of a black or brownish liquid to be taken by the teaspoonful four times a day. If this was not tolerated, a pink liquid medicine was substituted. The black medicine consisted of sugar, water extracts of red-clover blossoms, buckthorn, cascara, prickly-ash bark, poke root, berberis root, stillingia root, burdock, licorice and potassium iodide. The pink medicine was merely elixir of lactated pepsin with a quantity of potassium iodide.

In November, 1954, the use of a tablet was substituted for the black and pink liquids. Hoxsey proclaimed the tablet as "the greatest development" in medicine in recent years, stating that it was composed of the same ingredients as his black-liquid medicine.

Hoxsey claims to have inherited the "secret" of the cancer cure from his father, who in turn got it from Harry Hoxsey's grandfather, who, it is reported, learned of it when his horse grazed on certain herbs in a field and was thereby cured of cancer of the leg. The potassium iodide is apparently the grandson's innovation.

Hoxsey's Clinics have attracted thousands of innocent victims, many of whom are known to have forsaken proper medical treatment for Hoxsey's lure of a painless cure.

The Hoxsey menace will eventually pass as other fraudulent cures have passed. In the meanwhile, Harry M. Hoxsey unfortunately is still very much in evidence. The harried Food and Drug Administration is to be commended for its forthright stand. The legal procedure necessary to put a halt to such activities as Hoxsey's is, in the democratic process, long, involved and costly.

A forewarned and enlightened public, however, can precipitate the end of those who prey upon the unfortunate.

HIGHER EDUCATION IN NURSING: ANOTHER POINT OF VIEW

The *Journal*, in its issue of March 8, 1956, commented on the new program of the Yale School of Nursing, to start in the fall. Under this program the School will abandon its basic training course and shift its emphasis entirely to the upper brackets of higher education, preparing its students only for leadership in "teaching, practice and administration," in a course preparing exclusively for a degree of Master of Science in Nursing. In this respect at least the Yale School of Nursing will become another teachers college.

There are, however, those who, while they may not question too strongly the desirability of any university school's training nurses only for the highest echelon of service, do question the wisdom of such a school's abandoning entirely the basic training course.

A group of earnest undergraduates in the School of Nursing at Yale are apparently of this mind, believing that the basic training course has perhaps been underrated in the years since Annie W. Goodrich,

first dean of the School, expressed the philosophy that "nursing care is patient-centered care." They emphasize further her belief that each patient is a unique individual with various social, economic, emotional, spiritual and physiologic needs that should be impressed upon the student as part of this soon-to-be-neglected basic training. They envisage the School as perhaps planning to take its feet off the ground before it quite knows whether it can fly or not, and whither.

This group in all seriousness and with becoming respect even questions the complete understanding by the president and corporation of Yale University of the "essence of nursing education and the goals, aims and ideals of the nursing profession." Their criticism, however, is not so much of the failure of the Yale administration and of the general public to appreciate these aims and ideals as it is of the nursing profession in having failed to make them publicly known.

Efforts should be put under way, they believe, at Yale and elsewhere, to publicize these principles of education and of practice; of greater urgency is the nomination to the Yale Corporation of a medical member, sympathetic with the ideals and practices of nursing, who might interpret them to his fellow members.

CANADA WET

INVESTIGATIONS made by the Alcoholism Research Foundation of Ontario indicate an increase not only in the total number of alcoholics in Canada, but in the rate as well. Whereas the estimate for 1953 was 152,000 problem drinkers in the dominion, or 1670 per 100,000 population, the figure projected to the end of 1956 is 182,000, or 1850 per 100,000 Canadians aged twenty and older.

Both old and new figures are derived from the essentially British population of various counties in Ontario, no mention being made of the large French population in the province of Quebec, perhaps with different drinking habits. A joint study made in 1954 by the expert committees on mental health and alcoholism of the World Health Organization emphasized the difference in elbow-raising customs between northern countries where distilled liquor is rapidly imbibed, leading to amnesia and blackout, and those of gentler climes where wines and beers are sipped at more frequent intervals, resulting rather in somnolence and cirrhosis than in overt intoxication.*

The Canadian report, based as it is on an investigation confined to Ontario although extrapolated to cover the entire dominion, therefore makes no mention of the present drinking habits in Quebec — whether still those of sunny France or whether adapted to the more rigorous climate of the St. Lawrence valley and points north. So far as the ore is concerned from which the metal is smelted, Ontario and Quebec alike are capable of producing both the grain and the grape.

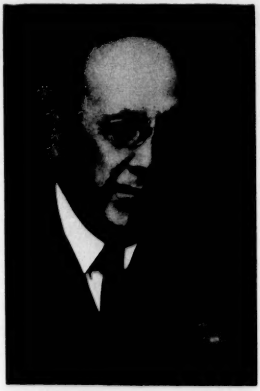
*Editorial. Problems of alcoholism. *New Eng. J. Med.* **251**:990, 1954.

Bust of Dr. Warren.—*It must be a matter of congratulation to the family of the late distinguished Dr. J. C. Warren that Ball Hughes has completed a fine likeness of him from sittings taken during the last two months. The bust was approved by the Doctor's family, and is a fine intellectual likeness, with a life-like expression, which this artist is always particularly happy in producing in his works. We presume there will be many calls for it in marble.* — Transcript
Boston M. & S. J. *May 15, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DR. JOSEPH H. PRATT

Dr. Joseph Hersey Pratt died on March 3, 1956, in the hospital in Boston that bears his name. He



was eighty-three years of age. He had lived a long, full, useful and happy life.

Dr. Pratt was born in Middleboro, Massachusetts,

on December 5, 1872. A graduate of Yale in 1894 and of Johns Hopkins University School of Medicine in 1898, he always spoke of his indebtedness to his great teachers in those schools, Chittenden, Welch and Osler. He came to Boston in 1898 as a pathologist, practiced and taught pathology for four years, working with William T. Councilman at the Harvard Medical School, and then went into the practice of internal medicine. Though it might entail great financial sacrifice, he always left his mornings free for investigative work and teaching.

Dr. Pratt appeared on the medical scene when scientific medicine in America was in its infancy. He left the medical scene when scientific medicine in this country had made such great strides as to place it in a position of world leadership. His driving energy, relentless probing, insatiable curiosity and boundless enthusiasm added much to the ferment that made American medicine bloom.

After some years at the Boston City Hospital, the Massachusetts General Hospital and the Peter Bent Brigham Hospital, he began a new career at the Boston Dispensary in 1927 at the age of fifty-five. Many of his major achievements date from that relatively advanced age. Ten years later his friend, Richard C. Cabot, wrote as follows:

> Why has Joe Pratt made so notable a success of his life? Besides his persistent and enthusiastic love for scientific truth, besides warmheartedness and the power to keep on growing, another quality has added force and effectiveness to his life,—his simplicity. He is all there in every act,—no conflicts or complexities waste his power. He does everything with the vigor of total concentration. If he is listening with a stethoscope or listening to your answer in conversation, he listens with all his might. He laughs whole-heartedly, he reads whole-heartedly, he works with all the energy that he possesses, he admires with every ounce of power that is in him. Few of my friends have such a talent for effective admiration. He secretes power and insight out of his admiration for great men.
>
> He has lived to build up, not to tear down. What a lot he has built!

That was written in 1937 — it might equally well have been written in 1956. He did indeed build a lot, spiritually, intellectually and scientifically — and physically, too, for much of the credit for the creation of the New England Medical Center as it is now known was his.

Those who have felt the spark of his genius, the force of his personality and the kindliness of his spirit will always cherish his memory.

His influence on American medicine through his creative accomplishments will long be felt. Dr. Pratt will live on as one of New England's medical giants.

S. P.

CORRESPONDENCE

ATTENDANCE AT SECTION LUNCHEONS

To the Editor: Having learned from past experience that many members of the Massachusetts Medical Society are unaware of their privileges regarding the Section luncheons that are held at the time of the annual meeting of the Society, would it not be appropriate in an early issue of the *Journal* to let all the practitioners know that they are welcome to attend any of the Section luncheons in which they are interested — that there are no exclusive lists for these luncheons, but that anyone may attend who is a member of the Massachusetts Medical Society?

I believe such information would clear up much of the misunderstanding that seems to exist at the time of the annual meeting.

GEORGE E. MORRIS, M.D., *Secretary*
Section of Industrial Health
Massachusetts Medical Society

Boston

LOCAL CORTISONE APPLICATION IN LEPROSY

To the Editor: An error for which we are responsible occurs in the Medical Progress report, "Treatment of Leprosy. I. Chemotherapy," in the January 5 issue of the *Journal*. The strength of cortisone used in local applications to the eye by Dr. James H. Allen, consulting ophthalmologist, Public Health Service Hospital, Carville, Louisiana (National Leprosarium), is much understated. It should be 0.5 per cent and not 5 mg. per 100 ml. as stated in the article.

We should appreciate a note of correction in the *Journal*.

JAMES A. DOULL, M.D.
ROLLA R. WOLCOTT, M.D.

Washington, D. C., and Carville, Louisiana

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held April 5, 1956, it was voted to suspend the registration of Dr. James J. Siragusa, Winter Park, Florida.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

Child Behavior. By Frances L. Ilg, M.D.; and Louise Bates Ames, Ph.D. 8°, cloth, 364 pp. New York: Harper and Brothers, 1955. $3.95.

This book from the Gesell Institute of Child Development, addressed to parents, is written in popular language. It covers such aspects of behavior as eating, sleeping, elimination, fears, discipline and the relation of the child to his parents, siblings and environment. Much of it concerns the handling of "behavior problems" in connection with these activities and others, and offers the sort of advice that every pediatrician spends much time giving to the parents of his young patients. The philosophy of the authors is in general that of permissive child rearing, but concessions are made to middle-of-the-road policies, and several divergent schools of thought are presented on certain highly controversial points. Many physicians will disagree with some of the suggestions authoritatively presented, such as that the parents of a three-year-old child who gets up in the middle of the night — roaming about downstairs (and possibly turning on the gas in the kitchen) — ought to accept such behavior blandly, as a phase that the child is going through and will shortly outgrow.

A more fundamental criticism concerns the authors' schematization of behavior patterns into cycles (smooth and consolidated at two years, breaking up at two and a half, rounded and balanced at three, inwardized at three and a half, expansive at four, inwardized-outwardized and "neurotic" at four and a half and then smooth and consolidated again at five, only to go through the same cycle twice more,

between five and ten, and ten and sixteen. The commanding position and stature of the Gesell Institute's work in the field of the child's motor development and acquisition of interests and activities in his environment can scarcely be challenged, but whether the same standardization can be applied to development of behavior is at least debatable. Certainly, the variation from one child to another might be expected to be far greater than the variation in the same child at the six-month to twelve-month intervals of his cycle of behavior patterns. The authors acknowledge this to some extent, but not explicitly enough to prevent many parent readers from accepting the cycle and patterns too rigidly.

Nevertheless, the book is recommended to pediatricians, general practitioners and others dealing widely with children, since it is certain to be read by the mothers of many of their patients, and the physicians concerned will therefore do well to be acquainted with the content. In the hands of some mothers, who can interpret and read selectively, this volume will provide useful and usually sound advice, at a length and in a degree of detail that the physician has not time to furnish. The unavoidable lack of individualization to fit a particular child in a particular family will greatly limit its usefulness to many mothers, however, and to avoid doing harm will require a good deal of interpretation and the taking with not a few grains of salt in the reading.

RICHMOND S. PAINE, M.D.

Peptic Ulcer: Diagnosis and treatment. By Clifford J. Barborka, M.D., M.S., D.Sc.; and E. Clinton Texter, Jr., M.D. 8°, cloth, 290 pp., with 33 illustrations. Boston: Little, Brown and Company, 1955. $7.00.

This new volume on a time-worn, ever-present subject, affords the student and practitioner a survey of the problem in all its complex phases. Since the authors are internists, and particularly interested in gastroenterology, it is natural that they include all the helpful methods of conservative treatment. The suggested dietary regimen is a combination of those found useful by previous writers on this subject and those used by the authors from their own vast clinical experience.

It is interesting that their summary of the surgical aspects of this problem coincides quite accurately with the present concepts of most surgeons. The chapter on gastric ulcer, with the better results from gastric resection, is valuable. Particularly important is the strong advocation of hospital treatment and evaluation in this group of patients. The authors point out quite forcefully the high percentage of malignant lesions that masquerade as benign gastric ulcer.

On the whole, this is a fine contribution at a time of considerable controversy concerning the management of peptic ulcer.

ARTHUR W. ALLEN, M.D.

Asclepiades: His life and writings: A translation of Cocchi's Life of Asclepiades and Gumpert's Fragments of Asclepiades. By Robert Montraville Green, M.D. 8°, cloth, 167 pp. New Haven: Elizabeth Licht, 1955. $6.00.

One of the most popular physicians in Rome in the first century B.C. was a Greek physician named Asclepiades. Little is known of his life and not much of his writings, but the principal data regarding his practice stems from the work of a Florentine physician in the middle of the eighteenth century named Antonio Cocchi, who spent years in collecting notes regarding Asclepiades. The results of his research were presumably published in an Italian edition. No copy of this book has ever been found, but an English translation was issued in London in 1762. This is not a very uncommon book. An Italian edition of the complete works of Cocchi was published in Milan in 1824, and the late Dr. Robert M. Green made a new English translation from it that now appears for the first time. In some respects it is superior to the previous one made by an unknown translator in 1762, but one misses the flavor of the eighteenth-century English, which seems particularly appropriate for this "most authentic account procurable."

A much rarer book on Asclepiades, consisting of the collected fragments of his writings so far as they could be found in references to him by other authors living at a later date, was compiled by Christian G. Gumpert at the University of Weimar, and published in three volumes (Weimar, 1794). Strangely enough, only one copy of this book appears to have survived in the Western Hemisphere. It is now in the Armed Forces Medical Library in Washington. Like the book by Cocchi, this book by Gumpert was also translated by Dr. Green, providing in readable form, for the first time in English, a volume that forms a connecting link between the ideas of Hippocrates and the practice of Galen. We are indebted to Dr. Sidney Licht and his wife, of New Haven, Connecticut, for the publishing of this book. At the same time we may note with sorrow the death of Dr. Robert M. Green, long an outstanding teacher of anatomy at the Harvard Medical School and in later life a translator of ancient medical books, among whose works this book is not the least considerable monument.

HENRY R. VIETS, M.D.

Histologische Geschwulstdiagnostik: Systematische Morphologie der menschlichen Geschwülste als Grundlage für die klinische Beurteiling. By A. v. Albertini. 4°, cloth, 544 pp., with 638 illustrations. Stuttgart: Georg Thieme, 1955. DM 98.40.- $23.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The author, a professor of pathology at the University of Zurich, presents a book on the histologic diagnosis of human tumors, excluding those arising in the central nervous system. The book is intended for all physicians dealing with neoplastic tissues rather than for pathologists alone.

The first part is devoted to a general discussion of neoplasms and their histogenesis. It attempts a nomenclature that differs slightly from the usual one. In particular, the author combines in his nomenclature histogenesis, differentiation, potentialities, origin and eponyms.

The second or special part is by far the more extensive and treats all major organ systems separately. Subjects, such as tumors of the testis, in which the author appears to have been particularly interested are dealt with in more detail, whereas the stomach and intestines, considering their importance, are too briefly considered. Each chapter is subdivided into epithelial and nonepithelial tumors. Benign and malignant neoplasms are taken up separately. The common lesions are abundantly and superbly illustrated. The pathologist reading this book would undoubtedly desire a more extensive discussion and illustration of uncommon lesions that cause him difficulty in diagnosis. The subject of the much discussed "carcinoma in situ," however, is treated extensively in the chapter on female genital organs. A reasonable, useful working nomenclature on this subject is presented. There is practically no discussion, however, on histogenesis or etiology of tumors although their prognosis, on the basis of histologic criteria, is often attempted.

In many details the author's opinion differs from that of American pathologists. For instance, cystosarcoma phylloides is categorically declared a benign lesion, and hydatidiform moles are still regarded as "mucoid degenerations" of the placental villi. In general, however, this distracts little from the value of the work, which can be recommended to students of neoplastic diseases.

The bibliography is naturally primarily European and unfortunately refers to textbooks and chapters in Henke–Lubarsch more often than to individual authors. Nevertheless, the author has made a sincere attempt to include some of the more recent English and American publications.

The publishers are to be congratulated for the excellence in production of text and black-and-white photographs.

KURT BENIRSCHKE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Management of Pain in Cancer. Edited by M. J. Schiffrin, Ph.D., assistant professor, Division of Anesthesiology, University of Illinois College of Medicine, and assistant director of clinical research, Hoffmann-La Roche, Incorporated, Chicago. With a foreword by Warren H. Cole, M.D., professor of surgery and head, Department of Surgery, University of Illinois College of Medicine. 12°, cloth, 245 pp., with 10 illustrations. Chicago: The Year Book Publishers, Incorporated, 1956. $4.50.

A Guide to Psychiatric Books: With some suggested reading lists. By Karl A. Menninger, M.D., director, Department of Education, Menninger Foundation, Topeka, Kansas. Second edition, revised. 8°, cloth, 157 pp. New York: Grune and Stratton, 1956. $4.75. (*Menninger Clinic Monograph Series* No. 7.)

Food Poisoning. By G. M. Dack, M.D. Third edition, revised and enlarged. 8°, cloth, 251 pp. Chicago: University of Chicago Press, 1956. $6.00. (University of Chicago Committee on Publications in Biology and Medicine.)

A Follow-up Study of World War II Prisoners of War. By Bernard M. Cohen, Ph.D., statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D.C.; and Maurice Z. Cooper, M.D., Department of Medicine and Surgery, Veterans Administration, Washington, D.C. 8°, cloth, 81 pp., with 5 illustrations and 43 tables. Washington, D.C.: Superintendent of Documents, Government Printing Office, 1955. $1.50. (*VA Medical Monograph.*)

Soranus' Gynecology. Translated with an introduction by Owsei Temkin, M.D. With the assistance of Nicholson J. Eastman, M.D., Ludwig Edelstein, Ph.D., and Alan F. Guttmacher, M.D. 8°, cloth, 258 pp. Baltimore: Johns Hopkins Press, 1956. $5.00.

Joint FAO/WHO Expert Committee on Meat Hygiene. First report. 8°, paper, 52 pp., with illustrations. Geneva: World Health Organization, 1955. $0.60, 3/6, or Sw. fr. 2. Also available in French and Spanish. (Publication No. 99, *World Health Organization Technical Report Series.*) (Distributed in the United States by Columbia University Press, New York City.)

Handbook of Medical Library Practice: With a bibliography of the reference works and histories in medicine and the allied sciences. Edited by Janet Doe and Mary Louise Marshall. 8°, cloth, 601 pp. Chicago: American Library Association, 1956. $10.00.

Mechanisms of Congenital Malformation: Proceedings of the Second Scientific Conference of the Association for the Aid of Crippled Children, June 15 and 16, 1954. S. R. M. Reynolds, M.D., Department of Embryology, Carnegie Institution of Washington, chairman; Harold Wolff, editor; and Joseph Dancis, M.D., Department of Pediatrics, New York University College of Medicine, and Clement A. Smith, M.D., Department of Pediatrics, Harvard Medical School, Editorial Committee. 8°, cloth, 137 pp., with 50 illustrations and 16 tables. New York: Association for the Aid of Crippled Children, 1954.

The Nature of Hypnosis. By Paul Schilder, M.D., Ph.D. Translated by Gerda Corvin. 8°, cloth, 204 pp. New York: International Universities Press, Incorporated, 1956. $4.00.

Joint Ligament Relaxation Treated by Fibro-Osseous Proliferation: With special reference to low back disability, trigger point pain and referred pain. By George Stuart Hackett, M.D., consulting surgeon, Mercy Hospital, Canton, Ohio. 8°, cloth, 97 pp., with 17 illustrations. Springfield, Illinois: Charles C Thomas, 1956. $4.75.

Advances in Pediatrics. Vol. 8. Edited by Samuel Z. Levine, M.D., Cornell University Medical College. 8°, cloth, 273 pp., with illustrations and tables. Chicago: The Year Book Publishers, Incorporated, 1956. $8.00.

Biochemical Mechanisms in Inflammation. By Valy Menkin, M.A., M.D., head, Department of Experimental Pathology, Agnes Barr Chase Foundation for Cancer Research, and associate professor of experimental pathology, Temple University School of Medicine. Second edition, completely revised. 8°, cloth, 438 pp., with 166 illustrations and 24 tables. Springfield, Illinois: Charles C Thomas, 1956. $9.50. (Publication No. 288, *American Lecture Series.*)

A Paris Surgeon's Story. By Charles F. Bove, M.D., K.L.H.; with Dana Lee Thomas. With a foreword by Leland Stowe. 8°, cloth, 306 pp. Boston: Little, Brown and Company, 1956. $4.50.

The Mysteries: Papers from the Eranos Yearbooks. Vol. 2. Edited by Joseph Campbell. 8°, cloth, 476 pp., with illustrations and plates. New York: Pantheon Books, Incorporated, 1955. $5.00. (*Bollingen Series* XXX; sponsored by and published for Bollingen Foundation.)

Pathologic Physiology: Mechanisms of disease. Edited by William A. Sodeman, M.D., professor of medicine and chairman, Department of Medicine, University of Missouri School of Medicine. Second edition. 8°, cloth, 963 pp., with 173 illustrations and 35 tables. Philadelphia: W. B. Saunders Company, 1956. $13.00.

Preventive Medicine in World War II: Personal health measures and immunization. Vol. 3. Colonel John Boyd Coates, Jr., M.C., editor-in-chief; Ebbe Curtis Hoff, Ph.D., M.D., editor for preventive medicine; and Phebe M. Hoff, M.A., assistant editor. 4°, cloth, 394 pp., with 5 illustrations, 29 tables and 5 charts. Washington, D.C.: Office of the Surgeon General, Department of the Army, 1955. $3.25. (Medical Department, United States Army.)

NONCLINICAL NOTES

EINSTEIN AWARDS

A neuropsychiatrist and a poet were the first recipients of the Albert Einstein commemorative awards for achievement in medicine and the humanities.

The poet is Carl Sandburg, and the physician is Stanley Cobb, former chief of the psychiatric service at the Massachusetts General Hospital and professor of neuropathology at Harvard Medical School. The announcement was made on April 10 by Dr. Samuel Belkin, president of Yeshiva University, which established the awards to mark the first anniversary of the death of Professor Einstein.

NOTICES

JEWISH MEMORIAL HOSPITAL

The Jewish Memorial Hospital will hold a Medical Staff Meeting at the hospital, Monday, May 28, at 8 p.m. Dr. Chester S. Keefer will give a talk entitled "Medical Care of Tomorrow."

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital is sponsoring a lecture to be given by Dr. Frederick A. Coller at the Dowling Amphitheater, Boston City Hospital, Tuesday, May 29, at 7 p.m.

Dr. Coller will speak on "Modern Surgical Treatment of Cancer of the Colon and Rectum."

NEW ENGLAND PEDIATRIC SOCIETY

The spring meeting of the New England Pediatric Society will be held at the Mary Fletcher Hospital, Burlington, Vermont, on Friday, June 15. Dr. Erwin Neter will speak on the topic "Etiologic Aspects of Infantile Diarrhea" at the evening meeting.

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

The tenth annual meeting of the American Electroencephalographic Society will be held at the Claridge Hotel, Atlantic City, New Jersey, June 15-17. Included on the program is a colloquium on "The History of Neurophysiology," on Friday evening, June 15, and a symposium on "Electroencephalography in the Diagnosis of Coma States," on Sunday morning, June 17.

SOCIETY MEETINGS AND CONFERENCES

May 10–29. Consultation Clinics for Crippled Children in Massachusetts. Page 819, issue of April 26.
May 14. Henry Jackson Lecture. Page 875, issue of May 3.
May 14–17. Armed Forces Institute of Pathology. Page 774, issue of April 19.
May 14–18. American Nurses' Association. Page 491, issue of March 8.
May 15. South End Medical Club. Page 824, issue of April 26.
May 16–18. American College of Cardiology. Page 773, issue of April 19.
May 18. New England Rheumatism Society. Page 875, issue of May 3.
May 22–24. Massachusetts Medical Society Annual Meeting. Page 868, issue of May 3.
May 23. Boston Branch, American Medical Women's Association. Page 773, issue of April 19.
May 28. Jewish Memorial Hospital. Notice above.
May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.
May 29. Boston City Hospital House Officers' Association. Notice above.
June 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.
June 4–6. Third National Cancer Conference. Page 876, issue of May 3.
June 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
June 6–10. American College of Chest Physicians. Page 876, issue of May 3.
June 9 and 10. Society for Investigative Dermatology. Page 876, issue of May 3.
June 10 and 11. American Gastroscopic Society. Page 875, issue of May 3.
June 15. New England Pediatric Society. Notice above.
June 15–17. American Electroencephalographic Society. Notice above.
June 18–20. American Neurological Association. Page 875, issue of May 3.
June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
June 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 17

THURSDAY, MAY 17

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Studies on the Formation of Collagen. Dr. Jerome Gross. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Electric Pacemaker in Cardiac Arrest. Dr. Paul M. Zoll. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, MAY 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, MAY 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MAY 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m. Carney Lecture Series. The Use of the Laboratory in the Management of Infections. Dr. Edward H. Kass. Lecture Hall, Carney Hospital, 2100 Dorchester Avenue, Dorchester.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. William Schwartz. Stearns Auditorium, New England Center Hospital.

(Concluded on page xxviii)